CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-411

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

EXCLUSIVITY SUMMARY

NDA # 22-411 SUPPL # 000 HFD # 130

Trade Name Oleptro Extended-Release Tablets

Generic Name trazodone hydrochloride

Applicant Name Labopharm Europe Limited

Approval Date, If Known 02/02/2010

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES ☒ NO ☐

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3,SE4, SE5, SE6, SE7, SE8

505(b)(2)

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES ☒ NO ☐

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

N/A

d) Did the applicant request exclusivity?

YES ☒ NO ☐

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

3 years

e) Has pediatric exclusivity been granted for this Active Moiety?

YES ☐ NO ☒

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

N/A

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES ☐ NO ☒

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES ☒ NO ☐

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# 018207 Desyrel

NDA# 071196 Trazodone Hydrochloride Tablets

NDA#

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES ☐ NO ☒

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.)
IF "YES," GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES ☒ NO ☐

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES ☒ NO ☐

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

N/A

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES ☒ NO ☐

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES ☐ NO ☒

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES ☐ NO ☒

If yes, explain:

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Clinical Study 04-ACL3-001

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES ☐ NO ☒

Investigation #2 YES ☐ NO ☐

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

N/A

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES ☐ NO ☒

Investigation #2 YES ☐ NO ☐

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

N/A

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

Clinical Study 04-ACL3-001

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1		!
		!
IND # 76,137	YES ☒	! NO ☐
		! Explain:

Investigation #2		!
		!
IND #	YES ☐	! NO ☐
		! Explain:

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1	!
	!
YES ☐	! NO ☐
Explain:	! Explain:

Investigation #2	!
	!
YES ☐	! NO ☐
Explain:	! Explain:

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES ☐ NO ☒

If yes, explain:

==========

Name of person completing form: Bill Bender, CDR USPHS
Title: Senior Regulatory Project Manager
Date: 01/08/2010

Name of Office/Division Director signing form: Thomas Laughren, MD
Title: Division Director, Division of Psychiatry Products

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22411	ORIG-1	LABOPHARM INC	TRAZODONE CONTRAMID OAD E-R CAPLET

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

WILLIAM H BENDER
02/02/2010

THOMAS P LAUGHREN
02/02/2010

PEDIATRIC PAGE
(Complete for all filed original applications and efficacy supplements)

NDA/BLA#: 22-411 Supplement Number: _____ NDA Supplement Type (e.g. SE5): _____

Division Name: Psychiatry Products PDUFA Goal Date: July 18, 2009 Stamp Date: 9/18/2008

Proprietary Name: Oleptro

Established/Generic Name: Trazodone Hydrochloride Extended-Release Caplets

Dosage Form: Extended-Release Caplet

Applicant/Sponsor: Labopharm Europe Limited

Indication(s) *previously approved* (please complete this question for supplements and Type 6 NDAs only):
(1) N/A
(2) _____
(3) _____
(4) _____

Pediatric use for each pediatric subpopulation must be addressed for each indication covered by current application under review. A Pediatric Page must be completed for each indication.

Number of indications for this pending application(s): 1
(Attach a completed Pediatric Page for each indication in current application.)

Indication: Major Depressive Disorder

Q1: Is this application in response to a PREA PMR? Yes ☐ Continue
No ☒ Please proceed to Question 2.

If Yes, NDA/BLA#: _____ Supplement #: _____ PMR #: _____

Does the division agree that this is a complete response to the PMR?

☐ Yes. Please proceed to Section D.

☐ No. Please proceed to Question 2 and complete the Pediatric Page, as applicable.

Q2: Does this application provide for (If yes, please check all categories that apply and proceed to the next question):

(a) NEW ☐ active ingredient(s) (includes new combination); ☐ indication(s); ☒ dosage form; ☐ dosing regimen; or ☐ route of administration?*

(b) ☐ No. PREA does not apply. **Skip to signature block.**

**** Note for CDER: SE5, SE6, and SE7 submissions may also trigger PREA.***

Q3: Does this indication have orphan designation?

☐ Yes. PREA does not apply. **Skip to signature block.**

☒ No. Please proceed to the next question.

Q4: Is there a full waiver for all pediatric age groups for this indication (check one)?

- ☐ Yes: (Complete Section A.)
- ☒ No: Please check all that apply:
  - ☒ Partial Waiver for selected pediatric subpopulations (Complete Sections B)
  - ☒ Deferred for some or all pediatric subpopulations (Complete Sections C)
  - ☐ Completed for some or all pediatric subpopulations (Complete Sections D)
  - ☐ Appropriately Labeled for some or all pediatric subpopulations (Complete Sections E)
  - ☐ Extrapolation in One or More Pediatric Age Groups (Complete Section F)

  (Please note that Section F may be used alone or in addition to Sections C, D, and/or E.)

Section A: Fully Waived Studies (for all pediatric age groups)

Reason(s) for full waiver: (**check, and attach a brief justification for the reason(s) selected**)

- ☐ Necessary studies would be impossible or highly impracticable because:
  - ☐ Disease/condition does not exist in children
  - ☐ Too few children with disease/condition to study
  - ☐ Other (e.g., patients geographically dispersed): _____
- ☐ Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients AND is not likely to be used in a substantial number of pediatric patients.
- ☐ Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- ☐ Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- ☐ Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)

☐ Justification attached.

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please complete another Pediatric Page for each indication. Otherwise, this Pediatric Page is complete and should be signed.

Section B: Partially Waived Studies (for selected pediatric subpopulations)

Check subpopulation(s) and reason for which studies are being partially waived (fill in applicable criteria below):

Note: If Neonate includes premature infants, list minimum and maximum age in "gestational age" (in weeks).

				Reason (see below for further detail):			
		minimum	maximum	Not feasible#	Not meaningful therapeutic benefit*	Ineffective or unsafe†	Formulation failedΔ
☒	Neonate	0 wk. 0 mo.	6 wk. 12 mo.	☐	☐	☐	☐
☐	Other	_yr. __mo.	_yr. __mo.	☐	☒	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐

Are the indicated age ranges (above) based on weight (kg)? ☒ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☒ No; ☐ Yes.

Reason(s) for partial waiver (**check reason** corresponding to the category checked above, and **attach a brief justification**):

Not feasible:

☐ Necessary studies would be impossible or highly impracticable because:

- ☐ Disease/condition does not exist in children
- ☐ Too few children with disease/condition to study
- ☐ Other (e.g., patients geographically dispersed): _____

***** Not meaningful therapeutic benefit:

☒ Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients in this/these pediatric subpopulation(s) AND is not likely to be used in a substantial number of pediatric patients in this/these pediatric subpopulation(s).

† Ineffective or unsafe:

☐ Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)

☐ Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)

☐ Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)

Δ Formulation failed:

☐ Applicant can demonstrate that reasonable attempts to produce a pediatric formulation necessary for this/these pediatric subpopulation(s) have failed. (*Note: A partial waiver on this ground may only cover the pediatric subpopulation(s) requiring that formulation. An applicant seeking a partial waiver on this ground must submit documentation detailing why a pediatric formulation cannot be developed. This submission will be posted on FDA's website if waiver is granted.)*

☐ Justification attached.

For those pediatric subpopulations for which studies have not been waived, there must be (1) corresponding study plans that have been deferred (if so, proceed to Sections C and complete the PeRC Pediatric Plan Template); (2) submitted studies that have been completed (if so, proceed to Section D and complete the PeRC Pediatric Assessment form); (3) additional studies in other age groups that are not needed because the drug is appropriately labeled in one or more pediatric subpopulations (if so, proceed to Section E); and/or (4) additional studies in other age groups that are not needed because efficacy is being extrapolated (if so,

proceed to Section F). Note that more than one of these options may apply for this indication to cover all of the pediatric subpopulations.

Section C: Deferred Studies (for selected pediatric subpopulations).

Check pediatric subpopulation(s) for which pediatric studies are being deferred (and fill in applicable reason below):

Deferrals (for each or all age groups):				**Reason for Deferral**			**Applicant Certification †**
Population		minimum	maximum	Ready for Approval in Adults	Need Additional Adult Safety or Efficacy Data	Other Appropriate Reason (specify below)*	Received
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	☐	☐	☐	☐
☒	Other	7 yr. 0 mo.	11 yr. 12 mo.	☐	☐	☐	☐
☒	Other	12 yr. 0 mo.	17 yr. 12 mo.	☒	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	All Pediatric Populations	0 yr. 0 mo.	16 yr. 11 mo.	☐	☐	☐	☐
	Date studies are due (mm/dd/yy): _____						

Are the indicated age ranges (above) based on weight (kg)? ☒ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☒ No; ☐ Yes.

* Other Reason: _____

† Note: Studies may only be deferred if an applicant submits a certification of grounds for deferring the studies, a description of the planned or ongoing studies, evidence that the studies are being conducted or will be conducted with due diligence and at the earliest possible time, and a timeline for the completion of the studies. If studies are deferred, on an annual basis applicant must submit information detailing the progress made in conducting the studies or, if no progress has been made, evidence and documentation that such studies will be conducted with due diligence and at the earliest possible time. This requirement should be communicated to the applicant in an appropriate manner (e.g., in an approval letter that specifies a required study as a post-marketing commitment.)

If all of the pediatric subpopulations have been covered through partial waivers and deferrals, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section D: Completed Studies (for some or all pediatric subpopulations).

Pediatric subpopulation(s) in which studies have been completed (check below):					
Population		minimum	maximum	PeRC Pediatric Assessment form attached?.	
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	Yes ☐	No ☐

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

Note: If there are no further pediatric subpopulations to cover based on partial waivers, deferrals and/or completed studies, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section E: Drug Appropriately Labeled (for some or all pediatric subpopulations):

Additional pediatric studies are not necessary in the following pediatric subpopulation(s) because product is appropriately labeled for the indication being reviewed:			
Population		minimum	maximum
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

If all pediatric subpopulations have been covered based on partial waivers, deferrals, completed studies, and/or existing appropriate labeling, this Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section F: Extrapolation from Other Adult and/or Pediatric Studies (for deferred and/or completed studies)

Note: Pediatric efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations if (and only if) (1) the course of the disease/condition AND (2) the effects of the product are sufficiently similar between the reference population and the pediatric subpopulation for which information will be extrapolated. Extrapolation of efficacy from studies in adults and/or other children usually requires supplementation with other information obtained from the target pediatric subpopulation, such as

pharmacokinetic and safety studies. Under the statute, safety cannot be extrapolated.

Pediatric studies are not necessary in the following pediatric subpopulation(s) because efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations:

Population		minimum	maximum	Extrapolated from:	
				Adult Studies?	Other Pediatric Studies?
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	☐	☐

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

Note: If extrapolating data from either adult or pediatric studies, a description of the scientific data supporting the extrapolation must be included in any pertinent reviews for the application.

If there are additional indications, please complete the attachment for each one of those indications. Otherwise, this Pediatric Page is complete and should be signed and entered into DFS or DARRTS as appropriate after clearance by PeRC.

This page was completed by:

{See appended electronic signature page}

Regulatory Project Manager

(Revised: 6/2008)

NOTE: If you have no other indications for this application, you may delete the attachments from this document.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

William Bender

4/17/2009 09:38:16 AM

PEDIATRIC PAGE
(Complete for all filed original applications and efficacy supplements)

NDA/BLA#: 22-411 Supplement Number: _____ NDA Supplement Type (e.g. SE5): _____

Division Name: Psychiatry Products PDUFA Goal Date: July 18, 2009 Stamp Date: 9/18/2008

Proprietary Name: Oleptro

Established/Generic Name: Trazodone Hydrochloride Extended-Release Caplets

Dosage Form: Extended-Release Caplet

Applicant/Sponsor: Labopharm Europe Limited

Indication(s) *previously approved* (please complete this question for supplements and Type 6 NDAs only):
(1) N/A
(2) _____
(3) _____
(4) _____

Pediatric use for each pediatric subpopulation must be addressed for each indication covered by current application under review. A Pediatric Page must be completed for each indication.

Number of indications for this pending application(s): 1
(Attach a completed Pediatric Page for each indication in current application.)

Indication: Major Depressive Disorder

Q1: Is this application in response to a PREA PMR? Yes ☐ Continue
No ☒ Please proceed to Question 2.

If Yes, NDA/BLA#: _____ Supplement #: _____ PMR #: _____

Does the division agree that this is a complete response to the PMR?

☐ Yes. Please proceed to Section D.

☐ No. Please proceed to Question 2 and complete the Pediatric Page, as applicable.

Q2: Does this application provide for (If yes, please check all categories that apply and proceed to the next question):

(a) NEW ☐ active ingredient(s) (includes new combination); ☐ indication(s); ☒ dosage form; ☐ dosing regimen; or ☐ route of administration?*

(b) ☐ No. PREA does not apply. **Skip to signature block.**

**** Note for CDER: SE5, SE6, and SE7 submissions may also trigger PREA.***

Q3: Does this indication have orphan designation?

☐ Yes. PREA does not apply. **Skip to signature block.**

☒ No. Please proceed to the next question.

Q4: Is there a full waiver for all pediatric age groups for this indication (check one)?

- ☐ Yes: (Complete Section A.)
- ☒ No: Please check all that apply:
  - ☒ Partial Waiver for selected pediatric subpopulations (Complete Sections B)
  - ☒ Deferred for some or all pediatric subpopulations (Complete Sections C)
  - ☐ Completed for some or all pediatric subpopulations (Complete Sections D)
  - ☐ Appropriately Labeled for some or all pediatric subpopulations (Complete Sections E)
  - ☐ Extrapolation in One or More Pediatric Age Groups (Complete Section F)

  (Please note that Section F may be used alone or in addition to Sections C, D, and/or E.)

Section A: Fully Waived Studies (for all pediatric age groups)

Reason(s) for full waiver: (**check, and attach a brief justification for the reason(s) selected**)

- ☐ Necessary studies would be impossible or highly impracticable because:
  - ☐ Disease/condition does not exist in children
  - ☐ Too few children with disease/condition to study
  - ☐ Other (e.g., patients geographically dispersed): _____
- ☐ Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients AND is not likely to be used in a substantial number of pediatric patients.
- ☐ Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- ☐ Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- ☐ Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)

☐ Justification attached.

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please complete another Pediatric Page for each indication. Otherwise, this Pediatric Page is complete and should be signed.

Section B: Partially Waived Studies (for selected pediatric subpopulations)

Check subpopulation(s) and reason for which studies are being partially waived (fill in applicable criteria below):

Note: If Neonate includes premature infants, list minimum and maximum age in "gestational age" (in weeks).

				Reason (see below for further detail):			
		minimum	maximum	Not feasible#	Not meaningful therapeutic benefit*	Ineffective or unsafe†	Formulation failedΔ
	Neonate	wk. mo.	wk. mo.	☐	☐	☐	☐
x	Other	1 yr. 0 mo.	6 yr. 12 mo.	☐	X	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐

Are the indicated age ranges (above) based on weight (kg)? ☒ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☒ No; ☐ Yes.

Reason(s) for partial waiver (**check reason** corresponding to the category checked above, and **attach a brief justification**):

Not feasible:

X Necessary studies would be impossible or highly impracticable because:

☐ Disease/condition does not exist in children

X Too few children with disease/condition to study

X Other (e.g., patients geographically dispersed): can't diagnose

***** Not meaningful therapeutic benefit:

Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients in this/these pediatric subpopulation(s) AND is not likely to be used in a substantial number of pediatric patients in this/these pediatric subpopulation(s).

† Ineffective or unsafe:

☐ Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)

☐ Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)

☐ Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)

Δ Formulation failed:

☐ Applicant can demonstrate that reasonable attempts to produce a pediatric formulation necessary for this/these pediatric subpopulation(s) have failed. (*Note: A partial waiver on this ground may only cover the pediatric subpopulation(s) requiring that formulation. An applicant seeking a partial waiver on this ground must submit documentation detailing why a pediatric formulation cannot be developed. This submission will be posted on FDA's website if waiver is granted.)*

☐ Justification attached.

For those pediatric subpopulations for which studies have not been waived, there must be (1) corresponding study plans that have been deferred (if so, proceed to Sections C and complete the PeRC Pediatric Plan Template); (2) submitted studies that have been completed (if so, proceed to Section D and complete the PeRC Pediatric Assessment form); (3) additional studies in other age groups that are not needed because the drug is appropriately labeled in one or more pediatric subpopulations (if so, proceed to Section E); and/or (4) additional studies in other age groups that are not needed because efficacy is being extrapolated (if so,

proceed to Section F). Note that more than one of these options may apply for this indication to cover all of the pediatric subpopulations.

Section C: Deferred Studies (for selected pediatric subpopulations).

Check pediatric subpopulation(s) for which pediatric studies are being deferred (and fill in applicable reason below):

Deferrals (for each or all age groups):				**Reason for Deferral**			**Applicant Certification †**
Population		minimum	maximum	Ready for Approval in Adults	Need Additional Adult Safety or Efficacy Data	Other Appropriate Reason (specify below)*	Received
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	☐	☐	☐	☐
☒	Other	7 yr. 0 mo.	11 yr. 12 mo.	X	☐	☐	☐
☒	Other	12 yr. 0 mo.	17 yr. 12 mo.	X	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	All Pediatric Populations	0 yr. 0 mo.	16 yr. 11 mo.	☐	☐	☐	☐
	Date studies are due (mm/dd/yy): _____						

Are the indicated age ranges (above) based on weight (kg)? ☒ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☒ No; ☐ Yes.

* Other Reason: _____

† Note: Studies may only be deferred if an applicant submits a certification of grounds for deferring the studies, a description of the planned or ongoing studies, evidence that the studies are being conducted or will be conducted with due diligence and at the earliest possible time, and a timeline for the completion of the studies. If studies are deferred, on an annual basis applicant must submit information detailing the progress made in conducting the studies or, if no progress has been made, evidence and documentation that such studies will be conducted with due diligence and at the earliest possible time. This requirement should be communicated to the applicant in an appropriate manner (e.g., in an approval letter that specifies a required study as a post-marketing commitment.)

If all of the pediatric subpopulations have been covered through partial waivers and deferrals, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section D: Completed Studies (for some or all pediatric subpopulations).

Pediatric subpopulation(s) in which studies have been completed (check below):					
Population		minimum	maximum	PeRC Pediatric Assessment form attached?.	
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	Yes ☐	No ☐

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

Note: If there are no further pediatric subpopulations to cover based on partial waivers, deferrals and/or completed studies, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section E: Drug Appropriately Labeled (for some or all pediatric subpopulations):

Additional pediatric studies are not necessary in the following pediatric subpopulation(s) because product is appropriately labeled for the indication being reviewed:			
Population		minimum	maximum
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

If all pediatric subpopulations have been covered based on partial waivers, deferrals, completed studies, and/or existing appropriate labeling, this Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section F: Extrapolation from Other Adult and/or Pediatric Studies (for deferred and/or completed studies)

Note: Pediatric efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations if (and only if) (1) the course of the disease/condition AND (2) the effects of the product are sufficiently similar between the reference population and the pediatric subpopulation for which information will be extrapolated. Extrapolation of efficacy from studies in adults and/or other children usually requires supplementation with other information obtained from the target pediatric subpopulation, such as

pharmacokinetic and safety studies. Under the statute, safety cannot be extrapolated.

Pediatric studies are not necessary in the following pediatric subpopulation(s) because efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations:

Population		minimum	maximum	Extrapolated from:	
				Adult Studies?	Other Pediatric Studies?
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	☐	☐

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

Note: If extrapolating data from either adult or pediatric studies, a description of the scientific data supporting the extrapolation must be included in any pertinent reviews for the application.

If there are additional indications, please complete the attachment for each one of those indications. Otherwise, this Pediatric Page is complete and should be signed and entered into DFS or DARRTS as appropriate after clearance by PeRC.

This page was completed by:

{See appended electronic signature page}

Regulatory Project Manager

(Revised: 6/2008)

NOTE: If you have no other indications for this application, you may delete the attachments from this document.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

William Bender

7/9/2009 03:36:38 PM

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION	**REQUEST FOR CONSULTATION**

TO *(Division/Office)*: Thomas Laughren, MD Division of Neurology Products	FROM(*Division/Office*) Nital Patel, Pharm.D., MBA Twyla Thompson, Pharm.D. Division of Drug Marketing, Advertising and Communications

DATE: 05/07/10	IND NO.	NDA NO. 022411	TYPE OF DOCUMENT: Launch Sales Aid and Patient Brochure	DATE OF DOCUMENTS: 04/26/10

NAME OF DRUG Oleptro® Trazodone hydrochloride extended-release tablets	PRIORITY CONSIDERATION YES	CLASSIFICATION OF DRUG: Anti-depressant	DESIRED COMPLETION DATE: 05/21/10

NAME OF FIRM: LABOPHARM

REASON FOR REQUEST

I. GENERAL

☐ NEW PROTOCOL	☐ PRE--NDA MEETING	☐ RESPONSE TO DEFICIENCY LETTER
☐ PROGRESS REPORT	☐ END OF PHASE II MEETING	☐ FINAL PRINTED LABELING
☐ NEW CORRESPONDENCE	☐ RESUBMISSION	☐ LABELING REVISION
☑ DRUG ADVERTISING	☐ SAFETY	☐ ORIGINAL NEW CORRESPONDENCE
☐ ADVERSE REACTION REPORT	☐ PAPER NDA	☐ FORMULATIVE REVIEW
☐ MANUFACTURING CHANGE/ADDITION	☐ CONTROL SUPPLEMENT	☐ OTHER *(SPECIFY BELOW)*:
☐ MEETING PLANNED BY		

COMMENTS/SPECIAL INSTRUCTIONS:

Please see questions below regarding proposed launch promotional materials for Oleptro. This consult, along with the promotional materials and references, will be delivered to the division's office. Please do not hesitate to contact us with any questions. Thanks.

Nital and Twyla
301-796-5331 or 301-796-4294

SIGNATURE OF REQUESTER Nital Patel, Pharm.D., MBA Twyla Thompson, Pharm.D.	METHOD OF DELIVERY (Check one) ☑ **MAIL (DFS and hand-carry)** ☐ FACSIMILE
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

3 pages withheld immediately after this page as B4 (TS/CCI)

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22411	ORIG-1	LABOPHARM INC	TRAZODONE CONTRAMID OAD E-R CAPLET

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

SHEILA K RYAN
05/07/2010
signing for Nital Patel

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION[1]

NDA # 22-411 BLA #	NDA Supplement # 000 BLA STN #	If NDA, Efficacy Supplement Type:
Proprietary Name: Oleptro Established/Proper Name: Trazodone Hydrochloride Extended-Release Tablets Dosage Form: Extended-Release Tablets		Applicant: Labopharm Europe Limited Agent for Applicant (if applicable): CanReg, Inc.
RPM: CDR William Bender		Division: Division of Psychiatry Products

NDAs:
NDA Application Type: ☐ 505(b)(1) ☒ 505(b)(2)
Efficacy Supplement: ☐ 505(b)(1) ☐ 505(b)(2)

(A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). Consult page 1 of the NDA Regulatory Filing Review for this application or Appendix A to this Action Package Checklist.)

505(b)(2) Original NDAs and 505(b)(2) NDA supplements:
Listed drug(s) referred to in 505(b)(2) application (include NDA/ANDA #(s) and drug name(s)):

Desyrel (NDA#018207) and Trazodone Hydrochloride Tablets (ANDA#071196)

Provide a brief explanation of how this product is different from the listed drug.

Extended-Release Formulation

☐ If no listed drug, check here and explain:

Prior to approval, review and confirm the information previously provided in Appendix B to the Regulatory Filing Review by re-checking the Orange Book for any new patents and pediatric exclusivity. If there are any changes in patents or exclusivity, notify the OND ADRA immediately and complete a new Appendix B of the Regulatory Filing Review.

☒ No changes ☐ Updated
Date of check:

If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.

<u>On the day of approval</u>, check the Orange Book again for any new patents or pediatric exclusivity.

❖ Actions	
• Proposed action • User Fee Goal Date is <u>February 11, 2010</u>	☒ AP ☐ TA ☐ CR
• Previous actions *(specify type and date for each action taken)*	☐ None CR (7/17/09)

[1] The **Application Information** section is (only) a checklist. The **Contents of Action Package** section (beginning on page 5) lists the documents to be included in the Action Package.

❖ If accelerated approval, were promotional materials received? Note: For accelerated approval (21 CFR 314.510/601.41), promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf). If not submitted, explain _____	☐ Received
❖ Application Characteristics [2]	

Review priority: ☒ Standard ☐ Priority
Chemical classification (new NDAs only):

☐ Fast Track
☐ Rolling Review
☐ Orphan drug designation
☐ Rx-to-OTC full switch
☐ Rx-to-OTC partial switch
☐ Direct-to-OTC

NDAs: Subpart H
☐ Accelerated approval (21 CFR 314.510)
☐ Restricted distribution (21 CFR 314.520)
Subpart I
☐ Approval based on animal studies

BLAs: Subpart E
☐ Accelerated approval (21 CFR 601.41)
☐ Restricted distribution (21 CFR 601.42)
Subpart H
☐ Approval based on animal studies

☐ Submitted in response to a PMR
☐ Submitted in response to a PMC
☐ Submitted in response to a Pediatric Written Request

Comments:

❖ BLAs only: *RMS-BLA Product Information Sheet for TBP* has been completed and forwarded to OBPS/DRM *(approvals only)*	☐ Yes, date
❖ BLAs only: is the product subject to official FDA lot release per 21 CFR 610.2 *(approvals only)*	☐ Yes ☐ No
❖ Public communications *(approvals only)*	
• Office of Executive Programs (OEP) liaison has been notified of action	☐ Yes ☐ No
• Press Office notified of action (by OEP)	☐ Yes ☐ No
• Indicate what types (if any) of information dissemination are anticipated	☒ None ☐ HHS Press Release ☐ FDA Talk Paper ☐ CDER Q&As ☐ Other

[2] Answer all questions in all sections in relation to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA. For example, if the application is a pending BLA supplement, then a new *RMS-BLA Product Information Sheet for TBP* must be completed.

❖ Exclusivity	
• Is approval of this application blocked by any type of exclusivity?	☒ No ☐ Yes
• NDAs and BLAs: Is there existing orphan drug exclusivity for the "same" drug or biologic for the proposed indication(s)? *Refer to 21 CFR 316.3(b)(13) for the definition of "same drug" for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification.*	☒ No ☐ Yes If, yes, NDA/BLA # and date exclusivity expires:
• (b)(2) NDAs only: Is there remaining 5-year exclusivity that would bar effective approval of a 505(b)(2) application)? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)*	☒ No ☐ Yes If yes, NDA # and date exclusivity expires:
• (b)(2) NDAs only: Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)*	☒ No ☐ Yes If yes, NDA # and date exclusivity expires:
• (b)(2) NDAs only: Is there remaining 6-month pediatric exclusivity that would bar effective approval of a 505(b)(2) application? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)*	☒ No ☐ Yes If yes, NDA # and date exclusivity expires:
• NDAs only: Is this a single enantiomer that falls under the 10-year approval limitation of 505(u)? *(Note that, even if the 10-year approval limitation period has not expired, the application may be tentatively approved if it is otherwise ready for approval.)*	☒ No ☐ Yes If yes, NDA # and date 10-year limitation expires:
❖ Patent Information (NDAs only)	
• Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought. If the drug is an old antibiotic, skip the Patent Certification questions.	☒ Verified ☐ Not applicable because drug is an old antibiotic.
• Patent Certification [505(b)(2) applications]: Verify that a certification was submitted for each patent for the listed drug(s) in the Orange Book and identify the type of certification submitted for each patent.	21 CFR 314.50(i)(1)(*i*)(A) ☒ Verified 21 CFR 314.50(i)(1) ☐ (ii) ☐ (iii)
• [505(b)(2) applications] If the application includes a **paragraph III** certification, it cannot be approved until the date that the patent to which the certification pertains expires (but may be tentatively approved if it is otherwise ready for approval).	☒ No paragraph III certification Date patent will expire
• [505(b)(2) applications] For **each paragraph IV** certification, verify that the applicant notified the NDA holder and patent owner(s) of its certification that the patent(s) is invalid, unenforceable, or will not be infringed (review documentation of notification by applicant and documentation of receipt of notice by patent owner and NDA holder). *(If the application does not include any paragraph IV certifications, mark "N/A" and skip to the next section below (*Summary Reviews*)).*	☒ N/A (no paragraph IV certification) ☐ Verified

- [505(b)(2) applications] For **each paragraph IV** certification, based on the questions below, determine whether a 30-month stay of approval is in effect due to patent infringement litigation.

  Answer the following questions for **each** paragraph IV certification:

  (1) Have 45 days passed since the patent owner's receipt of the applicant's notice of certification? ☐ Yes ☐ No

  (Note: The date that the patent owner received the applicant's notice of certification can be determined by checking the application. The applicant is required to amend its 505(b)(2) application to include documentation of this date (e.g., copy of return receipt or letter from recipient acknowledging its receipt of the notice) (see 21 CFR 314.52(e))).

  *If "**Yes**," skip to question (4) below. If "**No**," continue with question (2).*

  (2) Has the patent owner (or NDA holder, if it is an exclusive patent licensee) submitted a written waiver of its right to file a legal action for patent infringement after receiving the applicant's notice of certification, as provided for by 21 CFR 314.107(f)(3)? ☐ Yes ☐ No

  *If "**Yes,**" there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip the rest of the patent questions.*

  *If "**No**," continue with question (3).*

  (3) Has the patent owner, its representative, or the exclusive patent licensee filed a lawsuit for patent infringement against the applicant? ☐ Yes ☐ No

  (Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2))).

  *If "**No**," the patent owner (or NDA holder, if it is an exclusive patent licensee) has until the expiration of the 45-day period described in question (1) to waive its right to bring a patent infringement action or to bring such an action. After the 45-day period expires, continue with question (4) below.*

  (4) Did the patent owner (or NDA holder, if it is an exclusive patent licensee) submit a written waiver of its right to file a legal action for patent infringement within the 45-day period described in question (1), as provided for by 21 CFR 314.107(f)(3)? ☐ Yes ☐ No

  *If "**Yes,**" there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (*Summary Reviews*).*

  *If "**No**," continue with question (5).*

(5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the (b)(2) applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification? (Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced within the 45-day period). *If "**No**," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (*Summary Reviews*).* *If "**Yes**," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the OND ADRA and attach a summary of the response.*	☐ Yes ☐ No
CONTENTS OF ACTION PACKAGE	
❖ Copy of this Action Package Checklist[3]	Yes
Officer/Employee List	
❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list *(approvals only)*	☒ Included
Documentation of consent/non-consent by officers/employees	☒ Included
Action Letters	
❖ Copies of all action letters *(including approval letter with final labeling)*	Action(s) and date(s) Approval: 02/02/2010 Complete Response: 07/17/2009
Labeling	
❖ Package Insert *(write submission/communication date at upper right of first page of PI)*	
• Most recent draft labeling. If it is division-proposed labeling, it should be in track-changes format.	01/20/2010
• Original applicant-proposed labeling	09/18/2008
• Example of class labeling, if applicable	

[3] Fill in blanks with dates of reviews, letters, etc.

❖ Medication Guide/Patient Package Insert/Instructions for Use *(write submission/communication date at upper right of first page of each piece)*	☒ Medication Guide ☒ Patient Package Insert ☐ Instructions for Use ☐ None
• Most-recent draft labeling. If it is division-proposed labeling, it should be in ttrack-changes format.	01/20/2010
• Original applicant-proposed labeling	
• Example of class labeling, if applicable	
❖ Labels (**full color** carton and immediate-container labels) *(write submission/communication date on upper right of first page of each submission)*	
• Most-recent draft labeling	
❖ Proprietary Name • Acceptability/non-acceptability letter(s) *(indicate date(s))* • Review(s) *(indicate date(s))*	 Acceptable: 01/06/2010 Acceptable: 07/02/2009
❖ Labeling reviews *(indicate dates of reviews and meetings)*	☒ RPM ☒ DMEDP ☒ DRISK ☐ DDMAC ☐ CSS ☐ Other reviews
Administrative / Regulatory Documents	
❖ Administrative Reviews *(e.g., RPM Filing Review[4]/Memo of Filing Meeting) (indicate date of each review)*	RPM Filing Revies: 11/17/2008 Regulatory Filing Letter: 11/19/2008
❖ NDAs only: Exclusivity Summary *(signed by Division Director)*	☒ Included
❖ Application Integrity Policy (AIP) Status and Related Documents http://www fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm	
• Applicant in on the AIP	☐ Yes ☒ No
• This application is on the AIP o If yes, Center Director's Exception for Review memo *(indicate date)* o If yes, OC clearance for approval *(indicate date of clearance communication)*	☐ Yes ☒ No ☐ Not an AP action
❖ Pediatrics *(approvals only)* • Date reviewed by PeRC 05/13/2009 If PeRC review not necessary, explain: _____ • Pediatric Page *(approvals only, must be reviewed by PERC before finalized)*	 ☒ Included
❖ Debarment certification (original applications only): verified that qualifying language was not used in certification and that certifications from foreign applicants are cosigned by U.S. agent *(include certification)*	☒ Verified, statement is acceptable
❖ Outgoing communications *(letters (except action letters), emails, faxes, telecons)*	
❖ Internal memoranda, telecons, etc.	

[4] Filing reviews for scientific disciplines should be filed behind the respective discipline tab.

❖ Minutes of Meetings	
• Pre-Approval Safety Conference *(indicate date of mtg; approvals only)*	Not applicable
• Regulatory Briefing *(indicate date of mtg)*	☐ No mtg
• If not the first review cycle, any end-of-review meeting *(indicate date of mtg)*	☐ N/A or no mtg
• Pre-NDA/BLA meeting *(indicate date of mtg)*	☐ No mtg 03/14/2008
• EOP2 meeting *(indicate date of mtg)*	☐ No mtg
• Other milestone meetings (e.g., EOP2a, CMC pilot programs) *(indicates dates)*	
❖ Advisory Committee Meeting(s)	☒ No AC meeting
• Date(s) of Meeting(s)	
• 48-hour alert or minutes, if available *(do not include transcript)*	
Decisional and Summary Memos	
❖ Office Director Decisional Memo *(indicate date for each review)*	☒ None
Division Director Summary Review *(indicate date for each review)*	☐ None 02/02/2010
Cross-Discipline Team Leader Review *(indicate date for each review)*	☐ None
PMR/PMC Development Templates *(indicate total number)*	☐ None five
Clinical Information[5]	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) *(indicate date for each review)*	
• Clinical review(s) *(indicate date for each review)*	05/01/2009
• Social scientist review(s) (if OTC drug) *(indicate date for each review)*	☐ None
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here ☐ and include a review/memo explaining why not *(indicate date of review/memo)*	
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers *(indicate date of each review)*	☒ None
❖ Controlled Substance Staff review(s) and Scheduling Recommendation *(indicate date of each review)*	☒ Not applicable
❖ Risk Management • REMS Document and Supporting Statement *(indicate date(s) of submission(s))* • REMS Memo *(indicate date)* • Risk management review(s) and recommendations (including those by OSE and CSS) *(indicate date of each review and indicate location/date if incorporated into another review)*	01/14/2010 ☐ None 07/02/2009; 07/10/2009
❖ DSI Clinical Inspection Review Summary(ies) *(include copies of DSI letters to investigators)*	☐ None requested 05/27/2009

[5] Filing reviews should be filed with the discipline reviews.

Clinical Microbiology ☒ None	
❖ Clinical Microbiology Team Leader Review(s) *(indicate date for each review)*	☐ None
Clinical Microbiology Review(s) *(indicate date for each review)*	☐ None
Biostatistics ☐ None	
❖ Statistical Division Director Review(s) *(indicate date for each review)*	☐ None
Statistical Team Leader Review(s) *(indicate date for each review)*	☐ None
Statistical Review(s) *(indicate date for each review)*	☐ None 05/18/2009
Clinical Pharmacology ☐ None	
❖ Clinical Pharmacology Division Director Review(s) *(indicate date for each review)*	☐ None
Clinical Pharmacology Team Leader Review(s) *(indicate date for each review)*	☐ None
Clinical Pharmacology review(s) *(indicate date for each review)*	☐ None 05/22/2009
❖ DSI Clinical Pharmacology Inspection Review Summary *(include copies of DSI letters)*	☐ None
Nonclinical ☒ None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) *(indicate date for each review)*	☐ None
• Supervisory Review(s) *(indicate date for each review)*	☐ None
• Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	☐ None
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer *(indicate date for each review)*	☐ None
❖ Statistical review(s) of carcinogenicity studies *(indicate date for each review)*	☐ No carc
❖ ECAC/CAC report/memo of meeting	☐ None Included in P/T review, page
❖ DSI Nonclinical Inspection Review Summary *(include copies of DSI letters)*	☐ None requested
Product Quality ☐ None	
❖ Product Quality Discipline Reviews	
• ONDQA/OBP Division Director Review(s) *(indicate date for each review)*	☐ None
• Branch Chief/Team Leader Review(s) *(indicate date for each review)*	☐ None 12/11/2009: 07/14/2009
• Product quality review(s) including ONDQA biopharmaceutics reviews *(indicate date for each review)*	☐ None 12/11/2009: 07/14/2009 Biopharmaceuticals: 07/09/2009
❖ Microbiology Reviews ☐ NDAs: Microbiology reviews (sterility & pyrogenicity) (OPS/NDMS) *(indicate date of each review)* ☐ BLAs: Sterility assurance, microbiology, facilities reviews (DMPQ/MAPCB/BMT) *(indicate date of each review)*	☒ Not needed
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer *(indicate date of each review)*	☐ None

❖ Environmental Assessment (check one) (original and supplemental applications)	
☒ Categorical Exclusion *(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)*	
☐ Review & FONSI *(indicate date of review)*	
☐ Review & Environmental Impact Statement *(indicate date of each review)*	
❖ Facilities Review/Inspection	
☐ NDAs: Facilities inspections (include EER printout) *(date completed must be within **2 years** of action date)*	Date completed: 10/14/2009 ☒ Acceptable ☐ Withhold recommendation
☐ BLAs: TB-EER *(date of most recent TB-EER must be within **30 days** of action date)*	Date completed: ☐ Acceptable ☐ Withhold recommendation
❖ NDAs: Methods Validation *(check box only, do not include documents)*	☒ Completed ☐ Requested ☐ Not yet requested ☐ Not needed

Appendix A to Action Package Checklist

An NDA or NDA supplemental application is likely to be a 505(b)(2) application if:

(1) It relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application.
(2) **Or** it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval.
(3) **Or** it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations(see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

(1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies).
(2) **And** no additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application.
(3) **And** all other "criteria" are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

(1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2).
(2) **Or** the applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement.
(3) **Or** the applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your ODE's ADRA.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22411	ORIG-1	LABOPHARM INC	TRAZODONE CONTRAMID OAD E-R CAPLET

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/s/

WILLIAM H BENDER
02/02/2010

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: January 6, 2010

TO: NDA 022411

FROM: Kim Quaintance
Associate Director for Regulatory Affairs
Office of New Drugs

SUBJECT: Addendum to 505(b)(2) Assessment

This memorandum seeks to clarify the responses to questions 7 and 15 in the 505(b)(2) assessment for NDA 022411. The responses to questions 7 and 15 were completed by the Regulatory Project Manager based upon information as submitted in the 505(b)(2) application.

The applicant for NDA 022411, Labopharm Europe Limited (Labopharm), cited reliance on FDA's finding of safety and effectiveness for both Desyrel (trazodone hydrochloride) tablets (NDA 018207, applicant: Apothecon) and trazodone hydrochloride tablets (ANDA 071196, applicant: Apotex) to support approval of its 505(b)(2) application. However, this addendum clarifies that the applicant is in fact solely relying upon FDA's finding of safety and effectiveness for Desyrel (NDA 018207, applicant: Apothecon).

Desyrel is listed in the "Discontinued" section of the Orange Book, but was not withdrawn from sale for reasons of safety or effectiveness. Because Desyrel is no longer marketed, Labopharm conducted comparative bioavailability/bioequivalence trials with Apotex's trazodone hydrochloride tablets to establish the scientific appropriateness of reliance on FDA's finding of safety and effectiveness for Desyrel. This is appropriate because Apotex's ANDA 071196 for trazodone hydrochloride tablets cited Desyrel as its reference listed drug (RLD), was determined to be therapeutically equivalent to Desyrel, and subsequent to Desyrel's withdrawal from sale, was designated as the RLD for bioequivalence studies.

However, only a listed drug approved for safety and effectiveness under section 505(c) of the FFD&C Act (as distinguished from a drug approved in an ANDA under section 505(j) of the FFD&C Act) may be relied upon to support approval of a 505(b)(2) application. Accordingly, although Labopharm used Apotex's ANDA 071196 to "bridge" to FDA's finding of safety and effectiveness for Desyrel, this 505(b)(2) application solely relies upon FDA's finding of safety and effectiveness for Desyrel (NDA 018207).

The applicant did in fact state reliance on NDA 018207 and ANDA 071196 (as reflected in the response to question 7), however, as explained above, Labopharm is only relying upon the finding of safety and effectiveness for NDA 018207. Therefore, the patent certification for ANDA 071196 (no relevant patents) provided by the applicant is incorrect (see response to question 15) since an ANDA applicant is not permitted by statute to file patent information with FDA for listing in the Orange Book and thus there could be no requirement to submit a patent certification or statement for an ANDA product.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22411	ORIG-1	LABOPHARM INC	TRAZODONE CONTRAMID OAD E-R CAPLET

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/s/

KIM M Quaintance
01/06/2010

Bender, William

From: Bender, William
Sent: Friday, December 18, 2009 10:14 AM
To: 'Dhushy Thambipillai'
Subject: NDA 22-411 Oleptro

Follow Up Flag: Follow up
Flag Status: Purple

Attachments: Picture (Enhanced Metafile)

Hi Dhushy,

One more additional PMC would be the following:

DISSOLUTION METHOD & SPECIFICATIONS

We recommend the use of 50 -75 rpm in USP Type II apparatus. You are required to provide data using the appropriate condition at different speeds (rpms) to justify 150 rpm proposed dissolution methodology. We also recommend the following dissolution specification on an interim basis for one year; during this one year period, the sponsor is required to revise the dissolution method addressing the Agency's above mentioned comments and submit that to the Agency for review.

Strength	Dissolution Limits at each timepoint (%)			
	1 hr	6 hrs	12 hrs	20 hrs
150 mg	(b) (4)			
300 mg				

I beieve that we agreed to this previously, but wanted to make you aware that it would be included in the "Action Letter."

Please let me know if you have any questions.

Thanks and Merry Christmas!!!!
-Bill

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22411	ORIG-1	LABOPHARM INC	TRAZODONE CONTRAMID OAD E-R CAPLET

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/s/

WILLIAM H BENDER
01/05/2010

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 22-411 **INFORMATION REQUEST**

Canreg Inc.
Attention: Dhushy Thambipillai
450 North Lakeshore Drive
Mundelein, IL 60060

Dear Ms. Thambipillai:

Please refer to your August 10, 2009 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for trazodone hydrochloride tablets.

We are reviewing the Chemistry, Manufacturing and Controls section of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

As part of your drug product stability program, you performed a "half caplet in-use" stability study on batches (112542C, 112525C, 112655C, and 112657C). When comparing the results of these four batches in your in-use stability to those in your long-term stability study, it was observed that the average initial dissolution at the 6 and 12 hour time points for the half-tablets increases by (b) (4) of label claim for the 150 mg strengths and increases by (b) (4) of label claim for the 300 mg strengths. It is noted that this observation holds true for almost every half-tablet tested and not just for a few of the six. In addition, the results observed for the half-tablets are very close to your proposed specification limits (at 6h and 12h). Explain why there is such a disparity in the dissolution profiles for the half and whole tablets given that the release of the drug is controlled by (b) (4) Are these dissolution differences observed for all manufactured drug product batches? Do aged batches (e.g., batches stored for longer periods of time (say 12 months) and then broken show a similar trend)? Explain what factors are responsible for the observed dissolution differences. An additional concern is that breaking the tablets in an uncontrolled environment will result in tablets exhibiting more variability in dissolution than what was observed in your controlled setting. As a result, proper labeling instructions may be needed. Provide information to address the concerns highlighted above and the question on whether your half-tablets will remain within specification throughout the expiry.

If you have any questions, call Don Henry, Regulatory Project Manager, at (301) 796-4227.

Sincerely,

{See appended electronic signature page}

Ramesh Sood, Ph.D.
Branch Chief
Division of Pre-Marketing Assessment I
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22411	ORIG-1	LABOPHARM INC	TRAZODONE CONTRAMID OAD E-R CAPLET

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/s/

THOMAS F OLIVER
11/05/2009

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 22-411

ACKNOWLEDGE CLASS 2 RESPONSE

Labopharm Canada
Attention: Dhushy Thambipillai
Manager, Regulatory Affairs
450 North Lakeshore Drive
Mundelein, IL 60060

Dear Ms. Thambipillai:

We acknowledge receipt on August 11, 2009 of your August 10, 2009 resubmission to your new drug application for Oleptro (Trazodone Hydrochloride) Extended-Release Tablets, 150 mg and 300 mg for the treatment of Major Depressive Disorder.

We consider this a complete, class 2 response to our July 17, 2009 action letter. Therefore, the user fee goal date is February 11, 2010.

If you have any questions, please call me at (301) 796-2145.

Sincerely,

{See appended electronic signature page}

CDR William H. Bender
Senior Regulatory Project Manager
Division of Psychiatry Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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/s/

WILLIAM H BENDER
08/24/2009

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 22-411 **MEETING DENIED**

Canreg Inc.
Attention: Dhushy Thambipillai
450 North Lakeshore Drive
Mundelein, IL 60060

Dear Ms. Thambipillai:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for trazodone hydrochloride tablets.

We also refer to your July 22, 2009, correspondence requesting a meeting to discuss your response to the FDA 483 for one of the establishments. We are denying the meeting because any discussion would be premature since the inspection report is still under review.

If you have any questions, call me at (301) 796-4227.

Sincerely,

{See appended electronic signature page}

Don L. Henry
Regulatory Project Manager
Division of Pre-Marketing Assessment I
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

Linked Applications	Submission Type/Number	Sponsor Name	Drug Name / Subject
NDA 22411	GI 1		TRAZODONE CONTRAMID OAD E-R CAPLET

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/s/

DON L HENRY
08/06/2009

Bender, William

From: Bender, William
Sent: Tuesday, August 04, 2009 12:38 PM
To: 'Dhushy Thambipillai'
Subject: Second email that we spoke of regarding NDA 22-411, Oleptro

Good Day Dhushy,

Attached are comments regarding your REMS:

1. Revise your REMS goal as follows:

   The goal of this REMS is to inform patients about the serious risks associated with the use of OLEPTRO™ (trazodone hydrochloride) Extended- Release Tablets.

2. The Medication Guide distribution procedure does not provide sufficient details to determine whether it is in accordance with 21 CFR 208.24. Sufficient numbers of Medication Guides should be provided with the product such that a dispenser can provide one Medication Guide with each new or refilled prescription. We recommend that each packaging configuration contain enough Medication Guides so that one is provided for each "usual" or average dose. For example:

   - A minimum of 4 Medication Guides would be provided with a bottle of 100 for a product where the usual or average dose is 1 capsule/tablet daily, thus a monthly supply is 30 tablets.
   - A minimum of 1 Medication Guide would be provided with unit of use where it is expected that all tablets/capsules would be supplied to the patient.

3. We remind you of the requirement to comply with 21 CFR 208.24:

   - A required statement alerting the dispenser to provide the Medication Guide with the product must be on the carton and container of all strengths and formulations. We recommend the following language dependent upon whether the Medication Guide accompanies the product or is enclosed in the carton (for example, unit of use):

     "Dispense the enclosed Medication Guide to each patient." or

     "Dispense the accompanying Medication Guide to each patient."

4. The Timetable for Submission of Assessments of 18 months, 3 years, and 7 years is acceptable.

5. [redacted] (b) (4) However the goal of the REMS is to inform patients about the serious risks associated with the use of OLEPTRO™ (trazodone hydrochloride). To adequately evaluate the goal of this REMS, you need to assess patients' understanding of the serious risks and safe use information contained in the OLEPTRO™ (trazodone hydrochloride) Medication Guide. The results should be included in the REMS assessment at 18 months, 3 years, and 7 years.

   - You should submit for review, 90 days prior to implementation, the methodology and instrument that will be used to evaluate patients' understanding about the safe use of OLEPTRO™ (trazodone hydrochloride). If you plan to conduct this assessment using a survey, the submission should include, but not be limited to:
     - Sample size and confidence associated with that sample size
     - How the sample will be determined (selection criteria)
     - The expected number of patients to be surveyed

- How the participants will be recruited
- How and how often the surveys will be administered
- Explain controls used to minimize bias
- Explain controls used to compensate for the limitations associated with the methodology
- The survey instruments (questionnaires and/or moderator's guide).
- Any background information on testing survey questions and correlation to the messages in the Medication Guide.

6. See the appended OLEPTRO™ (trazodone hydrochloride) REMS proposal for additional track changes.

Please let us know if you have any questions.

(b) (4)

Linked Applications	Submission Type/Number	Sponsor Name	Drug Name / Subject
NDA 22411	GI 1	LABOPHARM INC	TRAZODONE CONTRAMID OAD E-R CAPLET

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/s/

WILLIAM H BENDER
09/02/2009

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION[1]		
NDA # 22-411 BLA #	NDA Supplement # 000 BLA STN #	If NDA, Efficacy Supplement Type:
Proprietary Name: Oleptro Established/Proper Name: Trazodone Hydrochloride Extended-Release Tablets Dosage Form: Extended-Release Tablets		Applicant: Labopharm Europe Limited Agent for Applicant (if applicable): CanReg Inc.
RPM: CDR William Bender		Division: Division of Psychiatry Products

NDAs:	505(b)(2) Original NDAs and 505(b)(2) NDA supplements:
NDA Application Type: ☐ 505(b)(1) X 505(b)(2) Efficacy Supplement: ☐ 505(b)(1) ☐ 505(b)(2) (A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). Consult page 1 of the NDA Regulatory Filing Review for this application or Appendix A to this Action Package Checklist.)	Listed drug(s) referred to in 505(b)(2) application (include NDA/ANDA #(s) and drug name(s)): Desyrel (NDA#018207) and Trazodone Hydrochloride Tablets (ANDA#071196) Provide a brief explanation of how this product is different from the listed drug. Extended-Release Formulation ☐ If no listed drug, check here and explain: **Prior to approval, review and confirm the information previously provided in Appendix B to the Regulatory Filing Review by re-checking the Orange Book for any new patents and pediatric exclusivity. If there are any changes in patents or exclusivity, notify the OND ADRA immediately and complete a new Appendix B of the Regulatory Filing Review.** X No changes ☐ Updated Date of check: 06/09/2009 **If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.** **On the day of approval, check the Orange Book again for any new patents or pediatric exclusivity.**

❖ User Fee Goal Date Action Goal Date (if different)	July 18, 2009
❖ Actions	
• Proposed action	☐ AP ☐ TA ☐ AE ☐ NA XCR
• Previous actions *(specify type and date for each action taken)*	X None

[1] The **Application Information** section is (only) a checklist. The **Contents of Action Package** section (beginning on page 5) lists the documents to be included in the Action Package.

❖ Promotional Materials *(accelerated approvals only)* Note: If accelerated approval (21 CFR 314.510/601.41), promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see guidance www fda.gov/cder/guidance/2197dft.pdf). If not submitted, explain _____	☐ Received

❖ Application[2] Characteristics	

Review priority: X Standard ☐ Priority
Chemical classification (new NDAs only):

☐ Fast Track
☐ Rolling Review
☐ Orphan drug designation
☐ Rx-to-OTC full switch
☐ Rx-to-OTC partial switch
☐ Direct-to-OTC

NDAs: Subpart H
☐ Accelerated approval (21 CFR 314.510)
☐ Restricted distribution (21 CFR 314.520)
Subpart I
☐ Approval based on animal studies

BLAs: Subpart E
☐ Accelerated approval (21 CFR 601.41)
☐ Restricted distribution (21 CFR 601.42)
Subpart H
☐ Approval based on animal studies

☐ Submitted in response to a PMR
☐ Submitted in response to a PMC

Comments: _____

❖ Date reviewed by PeRC *(required for approvals only)* If PeRC review not necessary, explain: _____	May 13, 2009
❖ BLAs only: *RMS-BLA Product Information Sheet for TBP* has been completed and forwarded to OBPS/DRM *(approvals only)*	☐ Yes, date
❖ BLAs only: is the product subject to official FDA lot release per 21 CFR 610.2 *(approvals only)*	☐ Yes ☐ No
❖ Public communications *(approvals only)*	
• Office of Executive Programs (OEP) liaison has been notified of action	☐ Yes ☐ No
• Press Office notified of action (by OEP)	☐ Yes ☐ No
• Indicate what types (if any) of information dissemination are anticipated	**X** None ☐ HHS Press Release ☐ FDA Talk Paper ☐ CDER Q&As ☐ Other

[2] All questions in all sections pertain to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA. For example, if the application is a pending BLA supplement, then a new *RMS-BLA Product Information Sheet for TBP* must be completed.

❖ Exclusivity	
• Is approval of this application blocked by any type of exclusivity?	X No ☐ Yes
• NDAs and BLAs: Is there existing orphan drug exclusivity for the "same" drug or biologic for the proposed indication(s)? *Refer to 21 CFR 316.3(b)(13) for the definition of "same drug" for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification.*	X No ☐ Yes If, yes, NDA/BLA # and date exclusivity expires:
• (b)(2) NDAs only: Is there remaining 5-year exclusivity that would bar effective approval of a 505(b)(2) application)? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)*	X No ☐ Yes If yes, NDA # and date exclusivity expires:
• (b)(2) NDAs only: Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)*	X No ☐ Yes If yes, NDA # and date exclusivity expires:
• (b)(2) NDAs only: Is there remaining 6-month pediatric exclusivity that would bar effective approval of a 505(b)(2) application? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)*	X No ☐ Yes If yes, NDA # and date exclusivity expires:
• NDAs only: Is this a single enantiomer that falls under the 10-year approval limitation of 505(u)? *(Note that, even if the 10-year approval limitation period has not expired, the application may be tentatively approved if it is otherwise ready for approval.)*	X No ☐ Yes If yes, NDA # and date 10-year limitation expires:
❖ Patent Information (NDAs only)	
• Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought. If the drug is an old antibiotic, skip the Patent Certification questions.	**X** Verified ☐ Not applicable because drug is an old antibiotic.
• Patent Certification [505(b)(2) applications]: Verify that a certification was submitted for each patent for the listed drug(s) in the Orange Book and identify the type of certification submitted for each patent.	21 CFR 314.50(i)(1)(*i*)(A) **X** Verified 21 CFR 314.50(i)(1) **X** (ii) ☐ **(**iii)
• [505(b)(2) applications] If the application includes a **paragraph III** certification, it cannot be approved until the date that the patent to which the certification pertains expires (but may be tentatively approved if it is otherwise ready for approval).	XNo paragraph III certification Date patent will expire
• [505(b)(2) applications] For **each paragraph IV** certification, verify that the applicant notified the NDA holder and patent owner(s) of its certification that the patent(s) is invalid, unenforceable, or will not be infringed (review documentation of notification by applicant and documentation of receipt of notice by patent owner and NDA holder). *(If the application does not include any paragraph IV certifications, mark "N/A" and skip to the next section below (*Summary Reviews*)).*	**X** N/A (no paragraph IV certification) ☐ Verified

- [505(b)(2) applications] For **each paragraph IV** certification, based on the questions below, determine whether a 30-month stay of approval is in effect due to patent infringement litigation.

  Not applicable... All patents are expired...

  Answer the following questions for **each** paragraph IV certification:

  (1) Have 45 days passed since the patent owner's receipt of the applicant's notice of certification? ☐ Yes ☐ No

  (Note: The date that the patent owner received the applicant's notice of certification can be determined by checking the application. The applicant is required to amend its 505(b)(2) application to include documentation of this date (e.g., copy of return receipt or letter from recipient acknowledging its receipt of the notice) (see 21 CFR 314.52(e))).

  *If "**Yes**," skip to question (4) below. If "**No**," continue with question (2).*

  (2) Has the patent owner (or NDA holder, if it is an exclusive patent licensee) submitted a written waiver of its right to file a legal action for patent infringement after receiving the applicant's notice of certification, as provided for by 21 CFR 314.107(f)(3)? ☐ Yes ☐ No

  *If "**Yes,**" there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip the rest of the patent questions.*

  *If "**No**," continue with question (3).*

  (3) Has the patent owner, its representative, or the exclusive patent licensee filed a lawsuit for patent infringement against the applicant? ☐ Yes ☐ No

  (Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2))).

  *If "**No**," the patent owner (or NDA holder, if it is an exclusive patent licensee) has until the expiration of the 45-day period described in question (1) to waive its right to bring a patent infringement action or to bring such an action. After the 45-day period expires, continue with question (4) below.*

  (4) Did the patent owner (or NDA holder, if it is an exclusive patent licensee) submit a written waiver of its right to file a legal action for patent infringement within the 45-day period described in question (1), as provided for by 21 CFR 314.107(f)(3)? ☐ Yes ☐ No

  *If "**Yes,**" there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (*Summary Reviews*).*

  *If "**No**," continue with question (5).*

(5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the (b)(2) applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification? (Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced within the 45-day period). *If "**No**," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (*Summary Reviews*).* *If "**Yes**," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the OND ADRA and attach a summary of the response.*	☐ Yes ☐ No
CONTENTS OF ACTION PACKAGE	
❖ Copy of this Action Package Checklist[3]	Yes
Officer/Employee List	
❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list *(approvals only)*	
Documentation of consent/non-consent by officers/employees	
Action Letters	
❖ Copies of all action letters *(including approval letter with final labeling)*	Action(s) and date(s) July 18, 2009
Labeling	
❖ Package Insert *(write submission/communication date at upper right of first page of PI)*	
• Most recent division-proposed labeling (only if generated after latest applicant submission of labeling)	
• Most recent submitted by applicant labeling (only if subsequent division labeling does not show applicant version)	
• Original applicant-proposed labeling	September 18, 2008
• Other relevant labeling (e.g., most recent 3 in class, class labeling), if applicable	
❖ Medication Guide/Patient Package Insert/Instructions for Use *(write submission/communication date at upper right of first page of each piece)*	X Medication Guide X Patient Package Insert ☐ Instructions for Use ☐ None

[3] Fill in blanks with dates of reviews, letters, etc.

• Most-recent division-proposed labeling (only if generated after latest applicant submission of labeling)	
• Most recent submitted by applicant labeling (only if subsequent division labeling does not show applicant version)	
• Original applicant-proposed labeling	September 18, 2008
• Other relevant labeling (e.g., most recent 3 in class, class labeling), if applicable	
❖ Labels (**full color** carton and immediate-container labels) *(write submission/communication date at upper right of first page of each submission)*	
• Most-recent division proposal for (only if generated after latest applicant submission)	
• Most recent applicant-proposed labeling	
❖ Labeling reviews *(indicate dates of reviews and meetings)*	X RPM X DMEDP X DRISK ☐ DDMAC ☐ CSS ☐ Other reviews
❖ Proprietary Name • Review(s) *(indicate date(s))* • Acceptability/non-acceptability letter(s) *(indicate date(s))*	 Acceptable 2/26/2009 Acceptable 07/12/2009
Administrative / Regulatory Documents	
❖ Administrative Reviews *(e.g., RPM Filing Review[4]/Memo of Filing Meeting) (indicate date of each review)*	RPM Filing Review-11/17/2008 Regulatory Filing Letter-11/19/2008
❖ NDAs only: Exclusivity Summary *(signed by Division Director)*	
❖ Application Integrity Policy (AIP) Status and Related Documents www fda.gov/ora/compliance_ref/aip_page html	
• Applicant in on the AIP	☐ Yes X No
• This application is on the AIP o If yes, Center Director's Exception for Review memo *(indicate date)* o If yes, OC clearance for approval *(indicate date of clearance communication)*	☐ Yes X No ☐ Not an AP action
❖ Pediatric Page *(approvals only, must be reviewed by PERC before finalized)*	X Included
❖ Debarment certification (original applications only): verified that qualifying language was not used in certification and that certifications from foreign applicants are cosigned by U.S. agent *(include certification)*	X Verified, statement is acceptable
❖ Postmarketing Requirement (PMR) Studies	☐ None
• Outgoing communications *(if located elsewhere in package, state where located)*	
• Incoming submissions/communications	
❖ Postmarketing Commitment (PMC) Studies	☐ None
• Outgoing Agency request for postmarketing commitments *(if located elsewhere in package, state where located)*	

[4] Filing reviews for other disciplines should be filed behind the discipline tab.

• Incoming submission documenting commitment	
❖ Outgoing communications *(letters (except previous action letters), emails, faxes, telecons)*	
❖ Internal memoranda, telecons, etc.	
❖ Minutes of Meetings	
• PeRC *(indicate date; approvals only)*	☐ Not applicable May 13,2009
• Pre-Approval Safety Conference *(indicate date; approvals only)*	☐ Not applicable
• Regulatory Briefing *(indicate date)*	☐ No mtg
• Pre-NDA/BLA meeting *(indicate date)*	☐ No mtg 2/28/2008
• EOP2 meeting *(indicate date)*	☐ No mtg
• Other (e.g., EOP2a, CMC pilot programs)	
❖ Advisory Committee Meeting(s)	X No AC meeting
• Date(s) of Meeting(s)	
• 48-hour alert or minutes, if available	
Decisional and Summary Memos	
❖ Office Director Decisional Memo *(indicate date for each review)*	☐ None
Division Director Summary Review *(indicate date for each review)*	☐ None
Cross-Discipline Team Leader Review *(indicate date for each review)*	☐ None
Clinical Information[5]	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) *(indicate date for each review)*	
• Clinical review(s) *(indicate date for each review)*	5-1-2009
• Social scientist review(s) (if OTC drug) *(indicate date for each review)*	☐ None
❖ Safety update review(s) *(indicate location/date if incorporated into another review)*	
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, review/memo explaining why not	
❖ Clinical reviews from other clinical areas/divisions/Centers *(indicate date of each review)*	☐ None
❖ Controlled Substance Staff review(s) and Scheduling Recommendation *(indicate date of each review)*	X Not needed
❖ Risk Management • Review(s) and recommendations (including those by OSE and CSS) *(indicate date of each review and indicate location/date if incorporated into another review)* • REMS Memo *(indicate date)* • REMS Document and Supporting Statement *(indicate date(s) of submission(s))*	☐ None
❖ DSI Clinical Inspection Review Summary(ies) *(include copies of DSI letters to investigators)*	☐ None requested 05-27-09
Clinical Microbiology ☐ None	
❖ Clinical Microbiology Team Leader Review(s) *(indicate date for each review)*	☐ None

[5] Filing reviews should be filed with the discipline reviews.

Clinical Microbiology Review(s) *(indicate date for each review)*	X None
Biostatistics ☐ None	
❖ Statistical Division Director Review(s) *(indicate date for each review)*	☐ None
Statistical Team Leader Review(s) *(indicate date for each review)*	☐ None
Statistical Review(s) *(indicate date for each review)*	☐ None 5-18-2009
Clinical Pharmacology ☐ None	
❖ Clinical Pharmacology Division Director Review(s) *(indicate date for each review)*	☐ None
Clinical Pharmacology Team Leader Review(s) *(indicate date for each review)*	☐ None
Clinical Pharmacology review(s) *(indicate date for each review)*	☐ None 5-22-09
❖ DSI Clinical Pharmacology Inspection Review Summary *(include copies of DSI letters)*	☐ None
Nonclinical ☐ None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) *(indicate date for each review)*	☐ None
• Supervisory Review(s) *(indicate date for each review)*	☐ None
• Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	☐ None
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer *(indicate date for each review)*	☐ None
❖ Statistical review(s) of carcinogenicity studies *(indicate date for each review)*	☐ No carc
❖ ECAC/CAC report/memo of meeting	☐ None Included in P/T review, page
❖ DSI Nonclinical Inspection Review Summary *(include copies of DSI letters)*	☐ None requested
CMC/Quality ☐ None	
❖ CMC/Quality Discipline Reviews	
• ONDQA/OBP Division Director Review(s) *(indicate date for each review)*	☐ None
• Branch Chief/Team Leader Review(s) *(indicate date for each review)*	☐ None 07/14/2009
• CMC/product quality review(s) *(indicate date for each review)*	☐ None 07/14/2009
• BLAs only: Facility information review(s) *(indicate dates)*	☐ None
❖ Microbiology Reviews • NDAs: Microbiology reviews (sterility & pyrogenicity) *(indicate date of each review)* • BLAs: Sterility assurance, product quality microbiology *(indicate date of each review)*	☐ Not needed
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer *(indicate date of each review)*	☐ None Biopharmacuetical Review 07/09/2009
❖ Environmental Assessment (check one) (original and supplemental applications)	
XCategorical Exclusion *(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)*	
☐ Review & FONSI *(indicate date of review)*	
☐ Review & Environmental Impact Statement *(indicate date of each review)*	

❖ NDAs: Methods Validation	☐ Completed ☐ Requested ☐ Not yet requested ☐ Not needed
❖ Facilities Review/Inspection	
• NDAs: Facilities inspections (include EER printout) *(date completed must be within 2 years of action date)*	Date completed: 07/08/2009 ☐ Acceptable **X** Withhold recommendation
• BLAs: o TBP-EER o Compliance Status Check (approvals only, both original and all supplemental applications except CBEs) *(date completed must be within 60 days prior to AP)*	 Date completed: ☐ Acceptable ☐ Withhold recommendation Date completed: ☐ Requested ☐ Accepted ☐ Hold

Appendix A to Action Package Checklist

An NDA or NDA supplemental application is likely to be a 505(b)(2) application if:

(1) It relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application.
(2) **Or** it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval.
(3) **Or** it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations(see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

(1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies).
(2) **And** no additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application.
(3) **And** all other "criteria" are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

(1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2).
(2) **Or** the applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement.
(3) **Or** the applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your ODE's ADRA.

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/s/

William Bender

7/15/2009 11:56:41 AM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 22-411

INFORMATION REQUEST LETTER

Canreg Inc.
Attention: Nicole Bruffato
450 North Lakeshore Drive
Chicago, IL 60060

Dear Dr. Bruffato:

Please refer to your September 18, 2008 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for trazodone hydrochloride tablets.

We are reviewing the Chemistry, Manufacturing and Controls section of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

1. You indicate that the average tablet weight includes [redacted] **(b) (4)**; however, it is not clear why the lower limit of the average weight should decrease for the shelf life specification as there are no expectations that the weight should decrease over the life of the product. Additionally, we consider monitoring of the tablet weight as method to be used to control the manufacturing process. As such, it is not necessary to monitor the tablet weight on stability. We recommend that you remove the test for tablet weight from the shelf life specification of the drug product.
2. DMF **(b) (4)** remains deficient for the manufacture and control of the drug substance, trazodone hydrochloride. The DMF holder has been informed of the deficiencies.

If you have any questions, call Don Henry, Regulatory Project Manager, at 301-796-4227.

Sincerely,

{See appended electronic signature page}

Ramesh Sood, Ph.D.
Branch Chief, Division of Pre-Marketing Assessment I
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

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/s/

Ramesh Sood

6/19/2009 02:01:42 PM

Bender, William

From: Bender, William
Sent: Tuesday, May 26, 2009 6:52 AM
To: 'Dhushy Thambipillai'
Subject: NDA 22-411

Hi Dhushy,

Based on your recent communications with the Agency regarding NDA 21-411 for trazodone hydrochloride extended-release tablets, you are unable to lower the specification for impurity (b) (4) from (b) (4) to the qualification threshold (or lower). However, you say that the drug substance supplier has toxicology information which might support the higher limit. Because qualification of that impurity (with that specification) would be required to support approval of your NDA, you should submit the reports for those studies as soon as possible. When we have received the study reports, we will determine whether this submission will extend the PDUFA date (7/18/09).

Please contact me with any questions.

Thanks,
Bill

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/s/

William Bender

5/26/2009 12:51:18 PM

CSO

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 22-411

INFORMATION REQUEST LETTER

Canreg Inc.
Attention: Nicole Bruffato
450 North Lakeshore Drive
Chicago, IL 60060

Dear Dr. Bruffato:

Please refer to your September 18, 2008 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for trazodone hydrochloride tablets.

We are reviewing the Chemistry, Manufacturing and Controls section of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

1. Submit full development and validation report for dissolution method describing the rational for selection of acid and buffer stage mediums, agitation speed, choice of apparatus and other parameters. The discussion should include discriminatory power of the method and the specification should mention the medium (pH) associated with each time point.

If you have any questions, call Don Henry, Regulatory Project Manager, at 301-796-4227.

Sincerely,

{See appended electronic signature page}

Ramesh Sood, Ph.D.
Branch Chief, Division of Pre-Marketing Assessment I
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

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/s/

Ramesh Sood

5/12/2009 09:12:08 AM

Bender, William

From: Bender, William
Sent: Friday, May 08, 2009 9:34 AM
To: 'Dhushy Thambipillai'
Cc: 'nbrufatto@canreginc.com'
Subject: NDA 22-411 Labeling Comments

Follow Up Flag: Follow up
Flag Status: Red

Good Day Dhushy,

We have the following comments regarding your labeling for Oleptro (Trazodone Hydrochloride) Extended-release tablets:

A. All Labels and Labeling
1. Revise all labels and labeling so that they accurately reflect the correct proposed proprietary name, Oleptro. Delete the terminology (b) (4)

2. The 150 mg and 300 mg strengths are similar in appearance. It is important to differentiate these labels and labeling to minimize the potential for selection error and
confirmation bias. Ensure that the labels and labeling for the 150 mg and 300 mg strengths are differentiated from one another.

B. Container Labels
Ensure that the unit-of-use bottles have a Child Resistant Closure (CRC) per the Poison Prevention Packaging Act (PPA) of 1970 to avoid accidental ingestion of Oleptro.

C. Blister Labels
The dosage form has been omitted from the blister labels. Insert the dosage form statement "Extended-release Caplet", so that it appears in conjunction with the established name.

D. Blister Carton Labeling
Include a statement on the blister carton labeling that provides the per tablet strength (e.g., XXX mg per tablet or each tablet contains XXX mg or add 'per tablet' to the current presentation of the strength. Our post-marketing surveillance demonstrates that omitting this statement is a source of confusion as patients are misled to believe that the entire contents of the blister equate to the stated strength dose.

Please feel free to contact me with any questions.

Thanks,
Bill

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/s/

William Bender
5/8/2009 12:43:45 PM
CSO

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 22-411 **INFORMATION REQUEST LETTER**

Canreg Inc.
Attention: Nicole Bruffato
450 North Lakeshore Drive
Chicago, IL 60060

Dear Dr. Bruffato:

Please refer to your September 18, 2008 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for trazodone hydrochloride tablets.

We are reviewing the Chemistry, Manufacturing and Controls section of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

1. In the dosage and administration section you indicate that the caplets should be swallowed whole and should not be chewed or crushed; however, in more than one place in the application you indicate that the caplets may be broken in half along the score line for dosing flexibility. Please explain.
2. Update the drug product specification to include an acceptance criterion for (b) (4)
3. Confirm that the method used for (b) (4) is USP or provide validation for this method.
4. Your acceptance criterion for hardness in the drug product should include an upper and a lower limit.
5. The proposed specification for (b) (4) is not acceptable as it appears not to be qualified and is above threshold of qualification (0.2%). Please lower the specification or complete non-clinical studies to qualify this impurity.
6. The proposed specification limit for "any single impurity" in the drug substance specification is NMT (b) (4) Be advised that threshold of identification is 0.1%. Accordingly, a limit of (b) (4) for any single impurity is not acceptable. Please lower your drug substance specification limit for "any single impurity" to an NMT 0.1% based on ICHQ3A.
7. The term "caplet" is not a recognized dosage form in the CDER Data Standards Manual. Please change the dosage form from Caplet to Tablet.
8. You have proposed two sets of specifications for the release and shelf life and stability for the drug product. Please be advised that the specification that you propose for shelf-life is your regulatory specification. Provide a consolidated drug product specification table with release and stability limits.
9. Provide a sample of the 150 mg and 300 mg drug product. Forward the samples to:

   Attention: Don Henry
   Office of New Drug Quality Assessment
   Center for Drug Evaluation and Research
   Food and Drug Administration
   10903 New Hampshire Avenue
   Silver Spring MD 20993-0002

10. DMF [redacted] (b) (4) is deficient for the manufacture and control of the drug substance, trazodone hydrochloride. The DMF holder is being notified of this by a separate letter which includes a list of the deficiencies

If you have any questions, call Don Henry, Regulatory Project Manager, at 301-796-4227.

Sincerely,

{See appended electronic signature page}

Ramesh Sood, Ph.D.
Branch Chief, Division of Pre-Marketing Assessment I
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

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/s/

Ramesh Sood

4/24/2009 08:48:25 AM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

TO *(Office/Division)*: Patrick Marroum CDER/OPS/ONDQA

FROM (*Name, Office/Division, and Phone Number of Requestor)*: Don Henry
Project Manager, ONDQA, 301-796-4227 on behalf of
Thomas Oliver/Sherita McLamore

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
March 20, 2009		22-411	NDA submission	September 18, 2008

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
trazodone hydrochloride	standard	Psychiatry	May 20, 2009

NAME OF FIRM: Labopharm

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE / ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE-NDA MEETING
- ☐ END-OF-PHASE 2a MEETING
- ☐ END-OF-PHASE 2 MEETING
- ☐ RESUBMISSION
- ☐ SAFETY / EFFICACY
- ☒ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☐ OTHER *(SPECIFY BELOW)*:

II. BIOMETRICS

- ☐ PRIORITY P NDA REVIEW
- ☐ END-OF-PHASE 2 MEETING
- ☐ CONTROLLED STUDIES
- ☐ PROTOCOL REVIEW
- ☐ OTHER (SPECIFY BELOW):
- ☐ CHEMISTRY REVIEW
- ☐ PHARMACOLOGY
- ☒ BIOPHARMACEUTICS
- ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☒ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE 4 STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL - BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG SAFETY

- ☐ PHASE 4 SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE, e.g., POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ NONCLINICAL

COMMENTS / SPECIAL INSTRUCTIONS: For this NDA, the dissolution method (including validation) and dissolution specification requires evaluation. The information can be found in Module 3, volume 6 and module 2, volume 1. Copies of these volumes will be forwarded.

SIGNATURE OF REQUESTOR	METHOD OF DELIVERY (Check one)
{See appended electronic signature page}	☒ DFS ☒ EMAIL ☐ MAIL ☐ HAND
PRINTED NAME AND SIGNATURE OF RECEIVER	PRINTED NAME AND SIGNATURE OF DELIVERER

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/s/

Ramesh Sood

3/23/2009 01:30:32 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville, MD 20857

IND 76,137

Labopharm Inc.
Attention: Becky Prokipcak, Ph.D.
450 North Lakeshore Drive
Mundelein, IL 60060

Dear Dr. Prokipcak:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Trazodone Contramid® OAD tablets.

We also refer to the meeting between representatives of your firm and the FDA on February 28, 2008. The purpose of the meeting was to discuss the planned contents of the NDA for extended release trazodone and to identify any possible problems.

A copy of the official minutes of the meeting is attached for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Kimberly Updegraff at (301)796-2201.

Sincerely,

{See appended electronic signature page}

Thomas Laughren, M.D.
Director
Division of Psychiatry Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Enclosure - Meeting Minutes

FDA Meeting Minutes
IND 76,137 Trazodone Contramid
Labopharm
Pre-NDA Meeting
February 28, 2008

Participants –
FDA

Thomas Laughren, MD	Director, Division of Psychiatry Products (DPP)
Mitchell Mathis, MD	Deputy Director
Gwen Zornberg, MD	Medical Team Leader
Karen Brugge, MD	Medical Reviewer, DPP
Linda Fossom, PhD	Pharmacology/Toxicology Reviewer
Shiny Mathew, PhD	Pharmacology/Toxicology Reviewer
Thomas Oliver, PhD	Pharmaceutical Assessment Lead
Sherita McLamore, PhD	Chemistry Reviewer
Ray Baweja, PhD	Clinical Pharmacology Team Leader
Kofi Kumi, PhD	Clinical Pharmacology/Biopharmaceutics Reviewer
Kimberly Updegraff, RPh, MS	Regulatory Project Manager

Sponsor

Sylvie Bouchard, MD, PhD	Senior Vice-President and Chief Medical Officer
Damon Smith, PhD	Senior Vice-President, Research and Development
Uwe Erbrich, PhD	Vice-President, Global Quality Assurance
Sybil Robertson, BSN	Vice-President, Regulatory Affairs, Pharmacovigilance and Medical Information.
Anna Rozova, MD, MSc	Director, Clinical Sciences
David Karhu, BSc	Director, Pharmacokinetics
Matteo Buttigieg, BPharm, MSc	Manager, Global CMC Regulatory Affairs
Magali Lurquin, BSc	Regulatory Affairs Manager
Becky Prokipcak, PhD	Consultant to Labopharm, CanReg Inc.

Background:

The purpose of this meeting is to confirm once again that this NDA for extended release trazodone can be filed as a 505(b)(2) application. The sponsor would also like to discuss the planned contents of the NDA and to identify any possible problems.

Labopharm's goal is to develop an extended-release formulation of trazodone hydrochloride. This formulation releases the drug over a 24-hour period, allowing once-a-day oral administration for the treatment of depression. It has been developed as 150 mg and 300 mg scored tablets containing Contramid®, a [redacted] modified starch, which controls the release of trazodone hydrochloride.

The NDA would include 3 PK studies and 1 short-term clinical efficacy and safety study. This latter trial was a randomized, 2-arm, double-blind, parallel group 8-

week flexible dose study. It was intended to include approximately n=380 patients with MDD. The flexible dose range of trazodone was 150-375 mg/day. The planned primary endpoint was change from baseline to endpoint on the HAMD-17 total score.

Questions:

NDA CONCEPT QUESTIONS

1. Labopharm intends to submit a New Drug Application for Trazodone Contramid® OAD under Section 505(b)(2) of the Federal Food, Drug and Cosmetic Act. We plan to submit the NDA in the CTD format. Does the Division concur that this is an acceptable approach?

   Preliminary Comments: *Yes.*

   Discussion at Meeting: *No further discussion.*

CHEMISTRY, MANUFACTURING AND CONTROLS

2. Trazodone Contramid® OAD extended-release 150 mg and 300 mg film-coated, scored tablets consist of a [redacted]. Labopharm intends to submit data from various batches manufactured for different purposes. An outline of our strategy for stability studies is provided in Section 11 (Chemistry, Manufacturing and Controls) of this briefing package. Labopharm would like to obtain confirmation that this strategy will be acceptable and sufficient to support the New Drug Application.

   Preliminary Comments: *We agree that your strategy is acceptable. Be advised that the stability data which is generated at the* [redacted] *will be considered your primary stability data. All other data will be reviewed as supportive stability data. The drug product expiry will be based on the quantity and quality of the primary stability data submitted in the application. Additionally, we recommend that you monitor* [redacted] *on stability and that you continue to evaluate multiple time points for dissolution throughout your stability studies as the evaluation of the dissolution data (specification and choice of timepoints) will be a review issue.*

   Discussion at Meeting: *We concurred with the Labopharm's use of* [redacted] *Labopharm stated that they will continue to test at all four time points (1h, 6h, 12h, and 24h) as part of their dissolution testing.*

3. Labopharm intends to qualify a second active substance supplier and a second final product manufacturer. Is it acceptable to submit additional information regarding those manufacturers during the review process?

Preliminary Comments: *This question will be discussed at the meeting.*

Discussion at Meeting: *Labopharm stated that, based on their timeframe, plans to add a second drug substance or drug product supplier were no longer being considered. We noted that all sites would need to be included in the original NDA and be ready for inspection at the time of NDA submission.*

Additional Issue: *As the tablets will be scored, we informed Labopharm that data will need to be submitted to support the storage of the half tablets. We recommended an in-use stability data study (e.g., a worst case scenario where the first tablet is broken and the unused half is the last dose used; such a study is typically performed in the largest count bottle). Labopharm stated that they were performing a study evaluating the performance of the half tablets.*

NON-CLINICAL

4. To support the New Drug Application for Trazodone Contramid® OAD extended-release tablets, Labopharm intends to cross reference the Agency's previous finding of safety regarding the Desyrel® NDA and submit an updated literature review with a summary of that literature. In addition, Labopharm will supply an overview of the toxicology of Contramid®. A detailed outline of the content of the submission is presented in this briefing package. Will the Division confirm that this data will be sufficient for the non-clinical sections of the Trazodone Contramid® OAD New Drug Application?

Preliminary Comments: *Yes; unless review of the application determines that additional studies are required to qualify impurities/degradants in drug substance or drug product.*

Discussion at Meeting: *We clarified that because the Sponsor intends to submit their NDA under 505(b)(2) for doses that are bio-equivalent to those approved for the reference drug (Desyrel®), for treatment of the same indication in the same patient population, we consider the non-clinical studies that supported the approval of the reference drug to be adequate to support the Sponsor's 505(b)(2) application. Consequently, no further non-clinical studies will be required unless review of the application determines that additional studies are required to qualify impurities/degradants in drug substance or drug product.*

PHARMACOKINETICS

5. Three pivotal BA/BE studies (steady state, dose proportionality and food effect) characterize the pharmacokinetic properties of the Trazodone Contramid® OAD formulation and will demonstrate similar exposure to the reference product (Apo-Trazodone) at steady state. Protocol synopses for the above pivotal pharmacokinetic studies are included in Appendix II.

   Can the Division confirm that the biopharmaceutics package consisting of these three pivotal BA/BE studies is sufficient to support the filing of our NDA?

   Preliminary Comments: *No*

   1) In addition to the proposed studies, one of the following studies should be conducted depending on whether the pharmacokinetics of trazodone is linear or non-linear.

   Linear kinetics:
   A fasting study comparing the MR product administered at the highest strength and as a single dose compared to the IR reference administered over the MR dosing interval.

   Or

   Non-linear kinetics:
   A fasting single dose study each comparing the highest strength of the MR product to the corresponding IR reference and the lowest strength of the MR product to the corresponding IR reference administered over the MR dosing interval.

   2) In the steady state multiple dose study, at least the following pharmacokinetic parameters should be determined: AUC(0-t), Cmax, Cmin.

   3) Dissolution: Dissolution testing in at least 3 media (e.g. pH 1.2, 4.5, 6.8., water) of each strength as follows: ½ unit, 2 x ½ units, 1 intact unit of each strength.

   Discussion at Meeting: *At the meeting, the sponsor provided additional information on the studies they have and are conducting and asked for comments. OCP stated that we will evaluate the additional information provided and give them a response in the final Meeting Minutes.*

   Post Meeting Comments

   1) The studies provided at the meeting will be adequate to describe the pharmacokinetics of Trazodone Contramid.

2) *If the sponsor intends to claim switchability between the Trazodone IR and Trazodone Contramid, in addition to the studies proposed, a study comparing Trazodone Contramid 75 mg (administered as a single dose) and Trazodone IR 75 mg (e.g., 25 mg administered 3 times a day) should be conducted. The report from this study should be included when the NDA is submitted for review.*
3) *The sponsor should conduct studies to investigate dose dumping in the presence of alcohol. The sponsor should perform in vitro dissolution studies for all Trazodone Contramid strengths using the final dissolution conditions with the addition of 0%, 5%, 10% and 20% of ethanol to the dissolution media.*
4) *To address the issue of whether the batch sizes are acceptable, the sponsor should provide, in the NDA submission, data comparing the pharmacokinetics after the Dose Proportionality 150 mg and 300 mg Study using caplets with batch size of caplets with the pharmacokinetics of the 150 mg and 300 mg strength in the Dose Proportionality 75 to 375 mg Study using batch size of caplets. Further, a comparison of the pharmacokinetics from the Single Dose 300 mg Trazodone Contramid OAD versus IR 100 mg TID using batch size of with the pharmacokinetics of the fasting arm of the Single Dose Food Effect 300 mg Trazodone Contramid OAD study using batch size caplets. A review of the data will determine whether the batches used in the initial studies are acceptable.*

CLINICAL SAFETY

6. For the safety database, it is our intent to cross-reference the Agency's previous findings of safety regarding the Desyrel® NDA and to submit the safety data from our Phase III clinical study (04ACL3-001) to support the filing of our NDA for Trazodone Contramid® OAD. A Clinical Safety Summary will be provided. However, no separate meta-analysis is planned as part of Module 5.

Does the Agency agree that this is acceptable?

Preliminary Comments: *Module 2.7.4 should include all new safety information from your new studies (3 PK studies and phase 3 clinical study). This section of the NDA should also include a review of the literature regarding trazodone, i.e., any references pertinent to safety. In particular, this review should address any concerns about cardiovascular toxicity with trazodone. The literature search should include search methods, a description of personnel and the credentials of those who conducted the search and the review. A review and summary of any available postmarketing safety data should be included in Module 2.7.4, as well.*

Module 5 should contain the study reports for all of your new studies.

Discussion at Meeting: *No further discussion.*

Conclusions:

Minutes will be provided to the sponsor. These minutes are the official minutes of the meeting. Labopharm is responsible for notifying us of any significant differences in understanding they have regarding the meeting outcomes.

Kimberly Updegraff, R.Ph.,M.S.
Regulatory Project Manager

Linked Applications	Sponsor Name	Drug Name
IND 76137	LABOPHARM CANADA	TRAZODONE CONTRAMID OAD

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/s/

THOMAS P LAUGHREN
03/14/2008

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 22-411

PROPRIETARY NAME REQUEST
- CONDITIONALLY ACCEPTABLE

Labopharm Canada
Attention: Dhushy Thambipillai
Regulatory Affairs Specialist
450 North Lakeshore Drive
Mundelein, IL 60060

Dear Ms. Thambipillai:

Please refer to your New Drug Application (NDA 22-411) dated September 18, 2008, received September 18, 2008, submitted pursuant to section 505(b) of the Federal Food, Drug, and Cosmetic Act, for Trazodone Hydrochloride Extended-Release Caplets 150 mg and 300 mg.

Additionally, your New Drug Application requested a review of your proposed proprietary name, Oleptro. We have completed our review of Oleptro and have concluded that it is acceptable.

Oleptro will be re-reviewed 90 days prior to the approval of the NDA. If we find the name unacceptable following the re-review, we will notify you.

If **any** of the proposed product characteristics as stated in your September 18, 2008 submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

If you have any questions, call Abolade (Bola) Adeolu, Regulatory Project Manager, at (301) 796-4264.

Sincerely,

{See appended electronic signature page}

Thomas Laughren, M.D.
Director
Division of Psychiatry Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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/s/

Thomas Laughren

3/6/2009 03:30:03 PM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

TO *(Office/Division)*: QT IRT Team/Devi Kozeli			FROM (*Name, Office/Division, and Phone Number of Requestor)*: HFD-130 (Division of Psychiatry Products); Tom Laughren, M.D.	
DATE 02/09/09	IND NO.	NDA NO. 22-411	TYPE OF DOCUMENT OSE review	DATE OF DOCUMENT 01/08/2009
NAME OF DRUG Oleptro(trazodone HCE extended-release caplet)	PRIORITY CONSIDERATION		CLASSIFICATION OF DRUG MDD	DESIRED COMPLETION DATE 03/20/2009

NAME OF FIRM: Labopharm

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE / ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE-NDA MEETING
- ☐ END-OF-PHASE 2a MEETING
- ☐ END-OF-PHASE 2 MEETING
- ☐ RESUBMISSION
- ☐ SAFETY / EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☒ OTHER *(SPECIFY BELOW)*:

II. BIOMETRICS

- ☐ PRIORITY P NDA REVIEW
- ☐ END-OF-PHASE 2 MEETING
- ☐ CONTROLLED STUDIES
- ☐ PROTOCOL REVIEW
- ☐ OTHER (SPECIFY BELOW):
- ☐ CHEMISTRY REVIEW
- ☐ PHARMACOLOGY
- ☐ BIOPHARMACEUTICS
- ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE 4 STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL - BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG SAFETY

- ☐ PHASE 4 SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE, e.g., POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ NONCLINICAL

COMMENTS / SPECIAL INSTRUCTIONS: Background: In an OSE review dated 8 January 2009 (attached) , the Division of Pharmacovigilance (DPV) identified several findings from the AERS database suggesting a possible risk of QT prolongation associated with trazodone: one case of sudden death, 16 cases of ventricular tachycardia (V-tach), 8 cases of Torsade de Pointe (TdP) and 16 cases of a prolonged QT interval. Sixty-eight per cent of the case series (TdP, V-tach, prolonged QT) were taking doses of 100 mg or less, off-label. The EBGM was greater than 4 for QT prolongation on ECG and greater than 2 for long QT syndrome and TdP.
Pre-clinical information for this drug is also suggestive of possible prolongation of the QTc interval, i.e., in a dog study, QTc was prolonged by 19%, and there was a dose-dependent inhibition of hERG in Xenopus oocytes (with slow, partial recovery).

Trazodone is a substrate for CYP3A4. DPV found the predominant risk factor for QT prolongation to be concomitant administration with either a drug metabolized by CYP3A4 and/or a drug labeled for QT prolongation.

Desyrel® labeling for the treatment of major depression recommends an initial dose of 150 mg/day in divided doses,

with dose increases in increments of 50 mg/day every 3 or 4 days, and a maximum recommended dose of 400 mg/day for outpatients and 600 mg/day for inpatients (in divided doses).
You should also be aware that the division is reviewing an NDA for a controlled release formulation of trazodone (NDA 22-411).

Question 1: Please review the attached data provided in the OSE review and relevant data, including ECG waveforms, from NDA 22-411 (Trazodone Extended Release Caplets for Unipolar Major Depression), available in the EDR. Please comment on the potential for trazodone to prolong the QT interval and/or induce cardiac dysrhythmias, and whether a thorough QT study is warranted.

Question 2: Please comment on whether there is adequate nonclinical evidence to support an association between trazodone and QT prolongation or cardiac dysrhythmias.

Dr. Victor Crentsil is the medical officer for this NDA. If you have any further questions you can contact me.

Attached is the review from OSE.

Thank you.

SIGNATURE OF REQUESTOR	METHOD OF DELIVERY (Check one)
Bill Bender Regulatory Project Manager 301-796-2145 William.bender@fda.hhs.gov	☒ DFS ☐ EMAIL ☐ MAIL ☐ HAND
PRINTED NAME AND SIGNATURE OF RECEIVER	PRINTED NAME AND SIGNATURE OF DELIVERER

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/s/

Jenna Lyndly
1/8/2009 01:41:30 PM
CSO

Min Chen
1/8/2009 04:17:41 PM
DRUG SAFETY OFFICE REVIEWER
Min Chen for KC Kwon

Mark Avigan
1/8/2009 04:40:01 PM
DRUG SAFETY OFFICE REVIEWER

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/s/

Thomas Laughren
2/9/2009 09:06:20 AM

Bender, William

From: Bender, William
Sent: Monday, November 17, 2008 12:11 PM
To: 'Dhushy Thambipillai'
Subject: NDA 22-411 Trazodone Hydrochloride Extended-Release Caplets

Good Day Ms. Thambipillai,

Your submission for NDA 22-411, Trazodone Hydrochloride Extended-Release Caplets, is filable with issues. An official "filable" letter with comments will be forthcoming.

If you have any questions, please feel free to contact me.

Thank you,
William H. Bender, R.Ph.
CDR, USPHS
FDA/CDER/Division of Psychiatry Products
Food and Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993
Phone: 301-796-2145
Fax: 301-796-9865
william.bender@fda.hhs.gov

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/s/

William Bender
11/17/2008 12:16:52 PM
CSO

505(b)(2) ASSESSMENT

Application Information		
NDA # 22-411	NDA Supplement #:S-	Efficacy Supplement Type SE-
Proprietary Name: Established/Proper Name: Trazodone Hydrochloride Extended-Release Caplets Dosage Form: Extended-Release Caplets Strengths: 150 mg and 300 mg		
Applicant: Labopharm Europe Limited		
Date of Receipt: September 18, 2008		
PDUFA Goal Date: July 18, 2009	Action Goal Date (if different):	
Proposed Indication(s): Major Depressive Disorder		

GENERAL INFORMATION

1. Is this application for a drug that is an "old" antibiotic as described in the Guidance to Industry, Repeal of Section 507 of the Federal Food, Drug and Cosmetic Act? (Certain antibiotics are not entitled to Hatch-Waxman patent listing and exclusivity benefits.)

YES ☐ NO X

*If "**YES**," proceed to question #3.*

2. Is this application for a recombinant or biologically-derived product and/or protein or peptide product?

YES ☐ NO X

*If "**YES** "contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*

INFORMATION PROVIDED VIA RELIANCE (LISTED DRUG OR LITERATURE)

3. List the information essential to the approval of the proposed drug that is provided by reliance on our previous finding of safety and efficacy for a listed drug or by reliance on published literature. *(If not clearly identified by the applicant, this information can usually be derived from annotated labeling.)*

Source of information (e.g., published literature, name of referenced product)	Information provided (e.g., pharmacokinetic data, or specific sections of labeling)
Labeling for Trazodone Hydrochloride Tablets, manufactured by (b) (4) and commercialized by Apotex Corp.	All sections of labeling.
Desyrel Prescribing Information by Bristol-Myers Squibb.	Please note that Desyrel has been discontinued for sale in the US since September, 2006 and the above mentioned Trazodone is the RLD.

4. Reliance on information regarding another product (whether a previously approved product or from published literature) must be scientifically appropriate. An applicant needs to provide a scientific "bridge" to demonstrate the relationship of the referenced and proposed products. Describe how the applicant bridged the proposed product to the referenced product(s). (Example: BA/BE studies)
   Bioavailability and Bioequivalence studies.

RELIANCE ON PUBLISHED LITERATURE

5. (a) Does the application rely on published literature to support the approval of the proposed drug product (i.e., the application *cannot* be approved without the published literature)?

   YES ☒ NO ☐

   *If "**NO**," proceed to question #6.*

   (b) Does any of the published literature necessary to support approval identify a specific (e.g., brand name) *listed* drug product?

   YES ☐ NO ☒

   *If "**NO**", proceed to question #6*
   *If "**YES**", list the listed drug(s) identified by name and answer question #5(c).*

   (c) Are the drug product(s) listed in (b) identified by the applicant as the listed drug(s)?

   YES ☒ NO ☐

RELIANCE ON LISTED DRUG(S)

Reliance on published literature which identifies a specific approved (listed) drug constitutes reliance on that listed drug. Please answer questions #6-10 accordingly.

6. Regardless of whether the applicant has explicitly referenced the listed drug(s), does the application **rely** on the finding of safety and effectiveness for one or more listed drugs (approved drugs) to support the approval of the proposed drug product (i.e., the application cannot be approved without this reliance)?

YES ☒ NO ☐

*If "**NO**," proceed to question #11.*

7. Name of listed drug(s) relied upon, and the NDA/ANDA #(s). Please indicate if the applicant explicitly identified the product as being relied upon (see note below):

Name of Drug	NDA/ANDA #	Did applicant specify reliance on the product? (Y/N)
Desyrel	018207	Y
Trazodone Hydrochloride Tablets	071196	Y

Applicants should specify reliance on the 356h, in the cover letter, and/or with their patent certification/statement. If you believe there is reliance on a listed product that has not been explicitly identified as such by the applicant, please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

8. If this is a supplement, does the supplement rely upon the same listed drug(s) as the original (b)(2) application?

YES ☐ NO ☐

*If "**NO**", please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*

9. Were any of the listed drug(s) relied upon for this application:
   a. Approved in a 505(b)(2) application?

YES ☐ NO ☒

*If "**YES**", please list which drug(s).*

Name of drug(s) approved in a 505(b)(2) application:

   b. Approved by the DESI process?

YES ☐ NO ☒

*If "**YES**", please list which drug(s).*

Name of drug(s) approved via the DESI process:

   c. Described in a monograph?

YES ☐ NO ☒

*If "**YES**", please list which drug(s).*

Name of drug(s) described in a monograph:

d. Discontinued from marketing?

YES ☒ NO ☐

*If "**YES**", please list which drug(s) and answer question d.1.*
*If "**NO**", proceed to question #10.*

Name of drug(s) discontinued from marketing: Desyrel

1. Were the products discontinued for reasons related to safety or effectiveness?

YES ☐ NO ☒

(Information regarding whether a drug has been discontinued from marketing for reasons of safety or effectiveness may be available in the Orange Book. Refer to section 1.11 for an explanation, and section 6.1 for the list of discontinued drugs. If a determination of the reason for discontinuation has not been published in the Federal Register (and noted in the Orange Book), you will need to research the archive file and/or consult with the review team. Do not rely solely on any statements made by the sponsor.)

10. Describe the change from the listed drug(s) relied upon to support this (b)(2) application (for example, "This application provides for a new indication, otitis media" or "This application provides for a change in dosage form, from capsule to solution").

This application provides for a new dosage form (extended release caplet).

The purpose of the following two questions is to determine if there is an approved drug product that is equivalent or very similar to the product proposed for approval that should be referenced as a listed drug in the pending application.

11. (a) Is there a pharmaceutical equivalent(s) to the product proposed in the 505(b)(2) application that is already approved (via an NDA or ANDA)?

*(**Pharmaceutical equivalents** are drug products in identical dosage forms that: **(1)** contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, or, in the case of modified release dosage forms that require a reservoir or overage or such forms as prefilled syringes where residual volume may vary, that deliver identical amounts of the active drug ingredient over the identical dosing period; **(2)** do not necessarily contain the same inactive ingredients; **and** **(3)** meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates. (21 CFR 320.1(c))*

Note that for proposed combinations of one or more previously approved drugs, a pharmaceutical equivalent must also be a combination of the same drugs.

YES ☐ NO ☒

*If "**NO**," to (a) proceed to question #12.*

(b) Is the pharmaceutical equivalent approved for the same indication for which the 505(b)(2) application is seeking approval?

YES ☐ ☐
NO

(c) Is the listed drug(s) referenced by the application a pharmaceutical equivalent?

YES ☐ NO ☐

*If "**YES**" and there are no additional pharmaceutical equivalents listed, proceed to question #13.*
*If "**NO**" or if there are additional pharmaceutical equivalents that are not referenced by the application, list the NDA pharmaceutical equivalent(s); you do not have to individually list all of the products approved as ANDAs, but please note that there are approved generics listed in the Orange Book. Please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*

Pharmaceutical equivalent(s):

12. (a) Is there a pharmaceutical alternative(s) already approved (via an NDA or ANDA)?

*(**Pharmaceutical alternatives** are drug products that contain the identical therapeutic moiety, or its precursor, but not necessarily in the same amount or dosage form or as the same salt or ester. Each such drug product individually meets either the identical or its own respective compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times and/or dissolution rates. (21 CFR 320.1(d)) Different dosage forms and strengths within a product line by a single manufacturer are thus pharmaceutical alternatives, as are extended-release products when compared with immediate- or standard-release formulations of the same active ingredient.)*

Note that for proposed combinations of one or more previously approved drugs, a pharmaceutical alternative must also be a combination of the same drugs.

YES X NO ☐

*If "**NO**", proceed to question #13.*

(b) Is the pharmaceutical alternative approved for the same indication for which the 505(b)(2) application is seeking approval?

YES X NO ☐

(c) Is the approved pharmaceutical alternative(s) referenced as the listed drug(s)?

YES X NO ☐

*If "**YES**" and there are no additional pharmaceutical alternatives listed, proceed to question #13.*
*If "**NO**" or if there are additional pharmaceutical alternatives that are not referenced by the application, list the NDA pharmaceutical alternative(s); you do not have to individually list all of the products approved as ANDAs, but please note that there are approved generics listed in the Orange Book. Contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*

Pharmaceutical alternative(s): Trazodone Hydrochloride tablets

PATENT CERTIFICATION/STATEMENTS

13. List the patent numbers of all patents listed in the Orange Book for the listed drug(s) for which our finding of safety and effectiveness is relied upon to support approval of the (b)(2) product.

    Listed drug/Patent number(s):

14. Did the applicant address (with an appropriate certification or statement) all of the patents listed in the Orange Book for the listed drug(s)?

    YES X NO ☐

    *If "**NO**", list which patents (and which listed drugs) were not addressed by the applicant.*

    Listed drug/Patent number(s):

15. Which of the following patent certifications does the application contain? *(Check all that apply and identify the patents to which each type of certification was made, as appropriate.)*

    ☐ No patent certifications are required (e.g., because application solely based on published literature that does not cite a specific innovator product or for an "old antibiotic" (see question 1.))

    ☐ 21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA. (Paragraph I certification)

    ☒ 21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired. (Paragraph II certification)

    Patent number(s):

    ☐ 21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire. (Paragraph III certification)

    Patent number(s):

    ☐ 21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted. (Paragraph IV certification)

    Patent number(s):

    If the application has been filed, did the applicant submit a signed certification stating that the NDA holder and patent owner(s) were notified the NDA was filed [21 CFR 314.52(b)]?

    YES ☐ NO ☐

Did the applicant submit documentation showing that the NDA holder and patent owner(s) received the notification [21 CFR 314.52(e)]? This is generally provided in the form of a registered mail receipt.

YES ☐ NO ☐

Date Received:

Has the applicant been sued for patent infringement (within 45-days of receipt of the notification listed above)? Note: you may need to call the applicant to verify this information.

YES ☐ NO ☐

☐ 21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the patent owner (must also submit certification under 21 CFR 314.50(i)(1)(i)(A)(4) above).

Patent number(s):
If the application has been filed, did the applicant submit a signed certification stating that the NDA holder and patent owner(s) were notified the NDA was filed [21 CFR 314.52(b)]?

YES ☐ NO ☐

Did the applicant submit documentation showing that the NDA holder and patent owner(s) received the notification [21 CFR 314.52(e)]? This is generally provided in the form of a registered mail receipt.

YES ☐ NO ☐

Date Received:

Has the applicant been sued for patent infringement (within 45-days of receipt of the notification listed above)? Note: you may need to call the applicant to verify this information.

YES ☐ NO ☐

☐ Written statement from patent owner that it consents to an immediate effective date of approval (applicant must also submit paragraph IV certification under 21 CFR 314.50(i)(1)(i)(A)(4) above).

Patent number(s):

X 21 CFR 314.50(i)(1)(ii): No relevant patents.

☐ 21 CFR 314.50(i)(1)(iii): The patent on the listed drug is a method of use patent and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent as described in the corresponding use code in the Orange Book. Applicant must provide a statement that the method of use patent does not claim any of the proposed indications. (Section viii statement)

Patent number(s):

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/s/

William Bender
11/17/2008 12:15:19 PM
CSO

NDA/BLA REGULATORY FILING REVIEW

(Including Memo of Filing Meeting)

<table>
<tr><th colspan="4">Application Information</th></tr>
<tr><td>NDA # 22-411
BLA#</td><td colspan="2">NDA Supplement #:S-
BLA STN #</td><td>Efficacy Supplement Type SE-</td></tr>
<tr><td colspan="4">Proprietary Name:
Established/Proper Name: Trazodone Hydrochloride Extended-Release Caplets
Dosage Form: Extended-Release Caplet
Strengths: 150 mg and 300 mg</td></tr>
<tr><td colspan="4">Applicant: Labopharm Europe Limited
Agent for Applicant (if applicable): CanReg Inc.</td></tr>
<tr><td colspan="4">Date of Application: September 18, 2008
Date of Receipt: September 18, 2008
Date clock started after UN:</td></tr>
<tr><td colspan="2">PDUFA Goal Date: July 18, 2009</td><td colspan="2">Action Goal Date (if different):</td></tr>
<tr><td colspan="2">Filing Date: November 17, 2008
Date of Filing Meeting: October 31, 2008</td><td colspan="2"></td></tr>
<tr><td colspan="4">Chemical Classification: (1,2,3 etc.) (original NDAs only) 3</td></tr>
<tr><td colspan="4">Proposed Indication(s): Major Depressive Disorder</td></tr>
<tr><td colspan="2">Type of Original NDA:
AND (if applicable)
Type of NDA Supplement:

Refer to Appendix A for further information.</td><td colspan="2">☐ 505(b)(1)
X 505(b)(2)
☐ 505(b)(1)
☐ 505(b)(2)</td></tr>
<tr><td colspan="2">Review Classification:

If the application includes a complete response to pediatric WR, review classification is Priority.

If a tropical disease Priority review voucher was submitted, review classification defaults to Priority.</td><td colspan="2">X Standard
☐ Priority

☐ Tropical disease Priority review voucher submitted</td></tr>
<tr><td colspan="4">Resubmission after withdrawal? ☐
Resubmission after refuse to file? ☐</td></tr>
<tr><td colspan="2">Part 3 Combination Product? ☐</td><td colspan="2">☐ Drug/Biologic
☐ Drug/Device
☐ Biologic/Device</td></tr>
<tr><td colspan="2">☐ Fast Track
☐ Rolling Review
☐ Orphan Designation

☐ Rx-to-OTC switch, Full
☐ Rx-to-OTC switch, Partial
☐ Direct-to-OTC

Other:</td><td colspan="2">☐ PMC response
☐ PMR response:
☐ FDAAA [505(o)]
☐ PREA deferred pediatric studies [21 CFR 314.55(b)/21 CFR 601.27(b)]
☐ Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41)
☐ Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)</td></tr>
</table>

Collaborative Review Division (*if OTC product*):	
List referenced IND Number(s): 76,137	
PDUFA and Action Goal dates correct in tracking system? ***If not, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.***	X YES ☐ NO
Are the proprietary, established/proper, and applicant names correct in tracking system? ***If not, ask the document room staff to make the corrections. Also, ask the document room staff to add the established name to the supporting IND(s) if not already entered into tracking system.***	X YES ☐ NO
Are all classification codes/flags (e.g. orphan, OTC drug, pediatric data) entered into tracking system? ***If not, ask the document room staff to make the appropriate entries.***	X YES ☐ NO
Application Integrity Policy	
Is the application affected by the Application Integrity Policy (AIP)? ***Check the AIP list at:*** ***http://www.fda.gov/ora/compliance_ref/aiplist.html*** **If yes**, explain: **If yes**, has OC/DMPQ been notified of the submission? **Comments**:	☐ YES X NO ☐ YES ☐ NO
User Fees	
Form 3397 (User Fee Cover Sheet) submitted	X YES ☐ NO
User Fee Status **Comments:**	X Paid ☐ Exempt (orphan, government) ☐ Waived (e.g., small business, public health) ☐ Not required
Note: *505(b)(2) applications are no longer exempt from user fees pursuant to the passage of FDAAA. It is expected that all 505(b) applications, whether 505(b)(1) or 505(b)(2), will require user fees unless otherwise waived or exempted (e.g., business waiver, orphan exemption).*	
Exclusivity	
Does another product have orphan exclusivity for the same indication? ***Check the Electronic Orange Book at:*** ***http://www.fda.gov/cder/ob/default.htm*** **If yes**, is the product considered to be the same product according to the orphan drug definition of sameness [21 CFR 316.3(b)(13)]?	☐ YES X NO ☐ YES ☐ NO

If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007) **Comments**:	
Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? ***(NDAs/NDA efficacy supplements only)*** ***Note:*** *An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.* **Comments**:	X YES # years requested: 3 NO
If the proposed product is a single enantiomer of a racemic drug previously approved for a different therapeutic use (***NDAs only***): Did the applicant (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b) request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)? ***If yes, contact Mary Ann Holovac, Director of Drug Information, OGD/DLPS/LRB.***	**X** Not applicable ☐ YES XNO
505(b)(2) (NDAs/NDA Efficacy Supplements only)	
	☐ **Not applicable**
1. Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?	☐ YES X NO
2. Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action less than that of the reference listed drug (RLD)? (see 21 CFR 314.54(b)(1)).	☐ YES X NO
3. Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug (see 21 CFR 314.54(b)(2))? ***Note:*** *If you answered yes to any of the above questions, the application may be refused for filing under 21 CFR 314.101(d)(9).*	☐ YES X NO

4. Is there unexpired exclusivity on the active moiety (e.g., 5-year, 3-year, orphan or pediatric exclusivity)? ***Check the Electronic Orange Book at: http://www.fda.gov/cder/ob/default.htm*** **If yes**, please list below:	☐ YES X NO

Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration

If there is unexpired, 5-year exclusivity remaining on the active moiety for the proposed drug product, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 108(b)(2). Unexpired, 3-year exclusivity will only block the approval, not the submission of a 505(b)(2) application.

Format and Content	
Do not check mixed submission if the only electronic component is the content of labeling (COL). **Comments**:	☐ All paper (except for COL) ☐ All electronic X Mixed (paper/electronic) ☐ CTD ☐ Non-CTD ☐ Mixed (CTD/non-CTD)
If mixed (paper/electronic) submission, which parts of the application are submitted in electronic format?	CRFs, Datasets, Annotated Labeling
If electronic submission: paper forms and certifications signed (non-CTD) or electronic forms and certifications signed (scanned or digital signature)(CTD)? ***Forms** include: 356h, patent information (3542a), financial disclosure (3454/3455), user fee cover sheet (3542a), and clinical trials (3674); **Certifications** include: debarment certification, patent certification(s), field copy certification, and pediatric certification.* **Comments**:	☐ YES ☐ NO
If electronic submission, does it follow the eCTD guidance? (*http://www.fda.gov/cder/guidance/7087rev.pdf*) **If not,** explain (e.g., waiver granted):	XYES ☐ NO

Form 356h: Is a signed form 356h included? ***If foreign applicant, <u>both</u> the applicant and the U.S. agent must sign the form.*** Are all establishments and their registration numbers listed on the form? **Comments**: We are obtaining the FEI# for a testing site in Canada.	X YES ☐ NO ☐ YES ☐ NO
Index: Does the submission contain an accurate comprehensive index? **Comments**:	X YES ☐ NO
Is the submission complete as required under 21 CFR 314.50 (*NDAs/NDA efficacy supplements*) or under 21 CFR 601.2 (*BLAs/BLA efficacy supplements*) including: ☐ legible ☐ English (or translated into English) ☐ pagination ☐ navigable hyperlinks (electronic submissions only) **If no**, explain:	X YES ☐ NO
Controlled substance/Product with abuse potential: Abuse Liability Assessment, including a proposal for scheduling, submitted? Consult sent to the Controlled Substance Staff? **Comments**:	X Not Applicable ☐ YES ☐ NO ☐ YES ☐ NO
BLAs/BLA efficacy supplements only: Companion application received if a shared or divided manufacturing arrangement? **If yes**, BLA #	 ☐ YES X NO
Patent Information (NDAs/NDA efficacy supplements only)	
Patent information submitted on form FDA 3542a? **Comments**:	X YES ☐ NO
Debarment Certification	
Correctly worded Debarment Certification with authorized signature? ***If foreign applicant, <u>both</u> the applicant and the U.S. Agent must***	XYES ☐ NO

sign the certification. ***Note:*** *Debarment Certification should use wording in FD&C Act section 306(k)(l) i.e.,"[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as, "To the best of my knowledge…"* **Comments**:	
Field Copy Certification (NDAs/NDA efficacy supplements only)	
Field Copy Certification: that it is a true copy of the CMC technical section (***applies to paper submissions only***) ***If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.***	☐ Not Applicable (*electronic submission or no CMC technical section*) X YES ☐ NO
Financial Disclosure	
Financial Disclosure forms included with authorized signature? ***Forms 3454 and/or 3455 must be included and must be signed by the APPLICANT, not an Agent.*** ***Note:*** *Financial disclosure is required for bioequivalence studies that are the basis for approval.* **Comments**:	X YES ☐ NO
Pediatrics	
PREA ***Note****: NDAs/BLAs/efficacy supplements for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.* Are the required pediatric assessment studies or a full waiver of pediatric studies included? **If no,** is a request for full waiver of pediatric studies OR a request for partial waiver/deferral and a pediatric plan included? • ***If no, request in 74-day letter.*** • **If yes**, does the application contain the certification(s) required under 21 CFR 314.55(b)(1), (c)(2), (c)(3)/21 CFR 601.27(b)(1), (c)(2), (c)(3) **Comments**:	☐ Not Applicable ☐ YES X NO X YES ☐ NO ☐ YES NO

<u>BPCA</u> (NDAs/NDA efficacy supplements only): Is this submission a complete response to a pediatric Written Request? ***If yes, contact PMHS (pediatric exclusivity determination by the Pediatric Exclusivity Board is needed).*** **Comments**:	☐ YES X NO
Prescription Labeling	
Check all types of labeling submitted. **Comments**:	☐ **Not applicable** X Package Insert (PI) ☐ Patient Package Insert (PPI) ☐ Instructions for Use X MedGuide X Carton labels X Immediate container labels ☐ Diluent ☐ Other (specify)
Is electronic Content of Labeling submitted in SPL format? ***If no, request in 74-day letter.*** **Comments**:	X YES ☐ NO
Package insert (PI) submitted in PLR format? **If no**, was a waiver or deferral requested before the application was received or in the submission? **If before**, what is the status of the request? ***If no, request in 74-day letter.*** **Comments**:	X YES ☐ NO ☐ YES ☐ NO
All labeling (PI, PPI, MedGuide, carton and immediate container labels) consulted to DDMAC? **Comments**:	X YES ☐ NO
MedGuide or PPI (plus PI) consulted to OSE/DRISK? (*send WORD version if available*) **Comments**:	☐ Not Applicable X YES ☐ NO
REMS consulted to OSE/DRISK? **Comments**: Not at the time of filing.	☐ Not Applicable ☐ YES X NO
Carton and immediate container labels, PI, PPI, and proprietary name (if any) sent to OSE/DMEDP? **Comments**:	☐ Not Applicable X YES ☐ NO

OTC Labeling	
Check all types of labeling submitted. **Comments**:	**X Not Applicable** ☐ Outer carton label ☐ Immediate container label ☐ Blister card ☐ Blister backing label ☐ Consumer Information Leaflet (CIL) ☐ Physician sample ☐ Consumer sample ☐ Other (specify)
Is electronic content of labeling submitted? ***If no, request in 74-day letter.*** **Comments**:	☐ YES ☐ NO
Are annotated specifications submitted for all stock keeping units (SKUs)? ***If no, request in 74-day letter.*** **Comments**:	☐ YES ☐ NO
If representative labeling is submitted, are all represented SKUs defined? ***If no, request in 74-day letter.*** **Comments**:	☐ YES ☐ NO
Proprietary name, all labeling/packaging, and current approved Rx PI (if switch) sent to OSE/DMEDP? **Comments**:	YES ☐ NO
Meeting Minutes/SPA Agreements	
End-of Phase 2 meeting(s)? ***If yes, distribute minutes before filing meeting.*** **Comments**:	X YES Date(s): ☐ NO
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? ***If yes, distribute minutes before filing meeting.*** **Comments**:	X YES Date(s): ☐ NO
Any Special Protocol Assessment (SPA) agreements? ***If yes, distribute letter and/or relevant minutes before filing meeting.*** **Comments**:	☐ YES Date(s): X NO

ATTACHMENT

MEMO OF FILING MEETING

DATE: October 30, 2008

NDA/BLA #: 22-411

PROPRIETARY/ESTABLISHED NAMES: Trazodone Hydrochloride Extended-Release Caplets

APPLICANT: Labopharm Europe Limited

BACKGROUND: This NDA is for an extended-release formulation.

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Bill Bender	Y
	CPMS/TL:	Paul David	N
Cross-Discipline Team Leader (CDTL)	Gwen Zornberg		Y
Clinical	Reviewer:	Victor Crentsil	Y
	TL:	Gwen Zornberg	Y
Social Scientist Review (*for OTC products*)	Reviewer:		
	TL:		
Labeling Review (*for OTC products*)	Reviewer:		
	TL:		
OSE	Reviewer:	Jinhee Lee from DMEPA	N
	TL:	Kellie Taylor	N
Clinical Microbiology (*for antimicrobial products*)	Reviewer:		
	TL:		

Clinical Pharmacology	Reviewer:	Kofi Kumi	Y
	TL:	Raman Baweja	Y
Biostatistics	Reviewer:	George Kordzakhia	Y
	TL:	Peiling Yang	N
Nonclinical (Pharmacology/Toxicology)	Reviewer:	Linda Fossom	Y
	TL:	Linda Fossom	Y
Statistics, carcinogenicity	Reviewer:		
	TL:		
Product Quality (CMC)	Reviewer:	McLamore, Sherita	N
	TL:	Thomas Oliver	Y
Facility (*for BLAs/BLA supplements*)	Reviewer:		
	TL:		
Microbiology, sterility (*for NDAs/NDA efficacy supplements*)	Reviewer:		
	TL:		
Bioresearch Monitoring (DSI)	Reviewer:		
	TL:		
Other reviewers			

OTHER ATTENDEES:

505(b)(2) filing issues? **If yes,** list issues: Filing issues to be communicated by Day 74.	☐ Not Applicable X YES ☐ NO
Per reviewers, are all parts in English or English translation? **If no**, explain:	X YES ☐ NO

Electronic Submission comments **List comments**:	☐ Not Applicable
CLINICAL **Comments**:	☐ Not Applicable X FILE ☐ REFUSE TO FILE X Review issues for 74-day letter
• Clinical study site(s) inspections(s) needed? **If no,** explain:	X YES ☐ NO
• Advisory Committee Meeting needed? **Comments**: ***If no, for an original NME or BLA application, include the reason. For example:*** o ***this drug/biologic is not the first in its class*** o ***the clinical study design was acceptable*** o ***the application did not raise significant safety or efficacy issues*** o ***the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease***	☐ YES Date if known: X NO ☐ To be determined Reason:
• If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? **Comments**:	☒ Not Applicable ☐ YES ☐ NO
CLINICAL MICROBIOLOGY **Comments**:	X Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
CLINICAL PHARMACOLOGY **Comments**:	☐ Not Applicable X FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• Clinical pharmacology study site(s) inspections(s)	☐ YES

needed?	X NO
BIOSTATISTICS **Comments**:	☐ Not Applicable X FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
NONCLINICAL (PHARMACOLOGY/TOXICOLOGY) **Comments**:	☐ Not Applicable X FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
PRODUCT QUALITY (CMC) **Comments**:	☐ Not Applicable X FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• Categorical exclusion for environmental assessment (EA) requested? **If no**, was a complete EA submitted? **If EA submitted**, consulted to EA officer (OPS)? **Comments**:	☐ Not Applicable X YES ☐ NO ☐ YES ☐ NO ☐ YES ☐ NO
• Establishment(s) ready for inspection? ▪ Establishment Evaluation Request (EER/TBP-EER) submitted to DMPQ? **Comments**:	☐ Not Applicable ☒ YES ☐ NO ☐ Not Applicable ☐ YES X NO
• Sterile product? **If yes**, was Microbiology Team consulted for validation of sterilization? (**NDAs/NDA supplements only**)	☐ YES X NO ☐ YES ☐ NO
FACILITY (BLAs only)	X Not Applicable ☐ FILE

Comments:	☐ REFUSE TO FILE X Review issues for 74-day letter

REGULATORY PROJECT MANAGEMENT
Signatory Authority: Thomas Laughren, MD, Director of Psychiatry Products **GRMP Timeline Milestones**: Meetings have been scheduled. **Comments**:

	REGULATORY CONCLUSIONS/DEFICIENCIES
☐	The application is unsuitable for filing. Explain why:
☒	The application, on its face, appears to be suitable for filing. ☐ No review issues have been identified for the 74-day letter. X Review issues have been identified for the 74-day letter. List (optional): X Standard Review ☐ Priority Review

	ACTIONS ITEMS
☒	Ensure that the review and chemical classification codes, as well as any other pertinent classification codes (e.g., orphan, OTC) are correctly entered into tracking system.
☐	If RTF action, notify everybody who already received a consult request, OSE PM., and Product Quality PM. Cancel EER/TBP-EER.
☐	If filed and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
☐	If BLA or priority review NDA, send 60-day letter.
☒	Send review issues/no review issues by day 74
☐	Other

Appendix A (NDA and NDA Supplements only)

NOTE: The term "original application" or "original NDA" as used in this appendix denotes the NDA submitted. It does not refer to the reference drug product or "reference listed drug."

An original application is likely to be a 505(b)(2) application if:

(1) it relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application,
(2) it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval, or
(3) it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations (see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

(1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies),

(2) No additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application, and.

(3) All other “criteria” are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely

for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

(1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2),

(2) The applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement, or

(3) The applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your OND ADRA or OND IO.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

William Bender
11/17/2008 09:13:01 AM
CSO

DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Food and Drug Administration
Rockville, MD 20857

FILING COMMUNICATION

NDA 22-411

Labopharm Canada
Attention: Dhushy Thambipillai
Regulatory Affairs Specialist
450 North Lakeshore Drive
Mundelein, IL 60060

Dear Ms. Thambipillai:

Please refer to your new drug application (NDA) dated September 18, 2008, received September 18, 2008, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act, for Trazodone Hydrochloride Extended-Release 150 mg and 300 mg caplets.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 314.101(a), this application is considered filed 60 days after the date we received your application. The review classification for this application is Standard. Therefore, the user fee goal date is July 18, 2009.

During our filing review of your application, we identified the following potential review issues and request that you submit the following information:

Clinical comments:

1. We note that you have provided data on the number of patients exposed to Trazodone Contramid® or placebo for specific intervals of duration of therapy. However, for determination of comparability of exposure to the Trazodone Contramid® and placebo arms of Study 04ACL3-001, we request data on the person-time exposure to Trazodone Contramid® and placebo.
2. We also observe that you stratified treatment related adverse events by age. For a more thorough exploration of the effect of demographic variables on treatment related adverse events, we request stratification of treatment related adverse events by other demographic variables such as gender, race, etc.
3. We acknowledge your inclusion of the listing of individual laboratory measurements by patients and your report that no change in laboratory values that occurred during the study were recorded as clinically relevant on the adverse event forms. To facilitate confirmation of your report, we request a summary of relevant laboratory data, with their mean change from baseline as well as percent outliers. Please include your criteria for determination of outliers.

4. We also request a summary of the mean change from baseline ECG parameters and percent outliers.
5. Please provide an analysis of the dose relatedness of adverse events reported during the conduct of Study 04ACL3-001.

We are providing the above comments to give you preliminary notice of potential review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review. Issues may be added, deleted, expanded upon, or modified as we review the application.

Please respond only to the above requests for additional information. While we anticipate that any response submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission.

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We note that you have not fulfilled the requirements. We acknowledge receipt of your request for a waiver of pediatric studies for this application for pediatric patients below the age of 7 and a deferral for pediatric children aged 7 years and older.

If you have any questions, call CDR William Bender, Senior Program Management Officer Consultant, at (301) 796-2145.

Sincerely,

{See appended electronic signature page}

Thomas Laughren, M.D.
Director
Division of Psychiatry Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Thomas Laughren
11/19/2008 12:56:08 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 22-411 **INFORMATION REQUEST LETTER**

Labopharm Canada
Attention: Dhushy Thambipillai
450 North Lakeshore Drive
Mundelein, IL 60060

Dear Ms. Thambipillai:

Please refer to your September 18, 2008 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Trazodone Hydrochloride extended-release caplets 150mg and 300mg.

We have the following comments from our brief overview of your proposed PLR labeling. These comments are regarding general formatting issues and are not all inclusive.

• The name (b) (4) is used throughout your proposed label. Please replace this name with your new proposed name.

• The following comments pertain to the "**HIGHLIGHTS OF PRESCRIBING INFORMATION**" section:

- Use the current language for the black box warning regarding suicidality.
- The drug name must be followed by drug's dosage form and route of administration.
- Under Contraindications, list known hazards and not theoretical possibilities (e.g., hypersensitivity to the drug).
- Use the verbatim statement in bold: **See 17 PATIENT COUNSELING INFORMATION and Medication Guide** for section 17.

• The following comments pertain to the "**FULL PRESCRIBING INFORMATION:CONTENTS"** section:

- Under the Warnings and Precaution section, do not separate the warning statements from the precaution statements (they are included together in the new format).
- Please include Subsection 8.2 Labor and Delivery in your proposed labeling.
- Please include Subsections 9.1 Controlled Substance; 9.2 Abuse; and 9.3 Dependence in your proposed labeling.
- Avoid using the word "General" as you have done in Section 17.2, General Information for Patients.

• The following comments pertain to the "**FULL PRESCRIBING INFORMATION"** section:

- Use the currently approved language for the boxed warning regarding suicidality.

- Under Section 3, Dosage Forms and Strengths, a description (Human Readable Text) of identifying characteristics of dosage forms is needed such as imprinting, scoring, shape, color, and coating.
- Under Section 4, Contraindications, list known hazards and not theoretical possibilities (i.e., hypersesitivity to the drug). If no Contraindications are known, this section must state "None."
- Under Section 5, Warnings and Precautions. a subheading should be used for each adverse reaction, syndrome, or constellation or reactions prioritized based on relative public health significance (do not separate warnings from precautions, they are included together). Also, list Warnings and Precautions in decreasing order of importance (i.e., reflecting the relative public health significance).
- Under Section 8, Use in Specific Populations, subsection 8.2, Labor and Delivery has been omitted. If any information required under this subsection is unknown, this section must state that the information is unknown.
- Under Secton 9, Drug Abuse and Dependence, include the following subsections: 9.1 Controlled Sustance; 9.2 Abuse; and 9.3 Dependence.
- Under Section 16, How Supplied/Storage and Handling, provide the units in which dosage form is ordinarily available for prescribing by practitioners (e.g., bottles of 100). Additionally, provide appropriate information to facilitate identification of dosage forms (i.e., shape, color, coating, scoring, imprinting and NDC number).
- Under Section 17, Patient Counseling Information, the reference [See FDA-Approved Medication Guide] should appear at the beginning of the Patient Counseling Information section. Avoid using the word "General" for the title of a subsection as you do for Section 17.2 (General Information for Patients).

As stated previously, the current language regarding the "Medication Guide for Antidepressant Drugs" must be incorporated into your labeling. Web site references and related information are provided below. Additionally, please note that all Medication Guide labeling must contain a toll free number to report adverse events to the Food and Drug Administration.

This web site serves as a reference for the Physician Labeling Rule (PLR):
http://www.fda.gov/cder/regulatory/physLabel/default.htm.

This web site contains the current language regarding the "Medication Guide for Antidepressant Drugs" which must be incorporated into your labeling:
http://www.fda.gov/cder/drug/antidepressants/default.htm..

This is the web site for the approved PLR labeling retrieved from the National Library of Medicine for venlafaxine (a recently approved 505(b2)) for your reference:
http://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?id=7776. Note: you must hit the "Ctrl" key and left click on the above mentioned web sites to view them.

We request a prompt written response in order to continue our evaluation of your NDA.

If you have any questions, call me at 301-796-2145.

Sincerely,

Thomas Laughren, M.D.
Director
Division of Psychiatry Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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/s/

Thomas Laughren

11/7/2008 03:57:02 PM

Bender, William

From: Bender, William
Sent: Friday, October 31, 2008 10:06 AM
To: 'Dhushy Thambipillai M.Sc, RAC'
Subject: NDA 22-411

Good Morning Dhushy,

Could you please provide us with the following information as soon as possible:

1) Provide the CFN #s for all drug substance manufacturing and testing sites along with the specific function performed at each site (i.e., "testing site" not specific enough).

2) Provide the CFN # for the Labopharm Inc. site (480 Boulevard Armand-Frappier, Laval, Quebec H7V 4B4).

Thank you,
Bill Bender

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/s/

William Bender

10/31/2008 02:37:18 PM

CSO

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 22-411

NDA ACKNOWLEDGMENT

Labopharm Canada
Attention: Dhushy Thambipillai
450 North Lakeshore Drive
Mundelein, IL 60060

Dear Ms. Thambipillari:

We have received your new drug application (NDA) submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA) for the following:

Name of Drug Product: Trazodone Contramid OAD Extended-Release Caplets, 150 mg and 300 mg

Date of Application: September 18, 2008

Date of Receipt: September 18, 2008

Our Reference Number: NDA 22-411

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on November 17, 2008 in accordance with 21 CFR 314.101(a).

If you have not already done so, promptly submit the content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at http://www.fda.gov/oc/datacouncil/spl.html. Failure to submit the content of labeling in SPL format may result in a refusal-to-file action under 21 CFR 314.101(d)(3). The content of labeling must conform to the content and format requirements of revised 21 CFR 201.56-57.

The NDA number provided above should be cited at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Psychiatry Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

All regulatory documents submitted in paper should be three-hole punched on the left side of the page and bound. The left margin should be at least three-fourths of an inch to assure text is not obscured in the fastened area. Standard paper size (8-1/2 by 11 inches) should be used; however, it may occasionally be necessary to use individual pages larger than standard paper size. Non-standard, large pages should be folded and mounted to allow the page to be opened for review without disassembling the jacket and refolded without damage when the volume is shelved. Shipping unbound documents may result in the loss of portions of the submission or an unnecessary delay in processing which could have an adverse impact on the review of the submission. For additional information, please see http:www.fda.gov/cder/ddms/binders.htm.

If you have any questions, call me at (301) 796-2145.

Sincerely,

{See appended electronic signature page}

CDR Bill Bender, R.Ph.
Regulatory Project Manager
Division of Psychiatry Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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/s/

William Bender

9/25/2008 01:02:37 PM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADM NISTRATION

REQUEST FOR CONSULTATION

TO *(Division/Office)*:	FROM:
OSE/DRISK Attn: Mary Dempsey	OND/ODE1/DPP HFD-130

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
09/24/08		22-411	Risk MAPP	09/18/2008

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
Trazodone Contramid OAD Extended-Release caplets	**PDUFA Goal Date: 07/18/09**	Major Depressive Disorder	

NAME OF FIRM: Labopharm

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE/ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE--NDA MEETING
- ☐ END OF PHASE II MEETING
- ☐ RESUBMISSION
- X SAFETY/EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☐ OTHER *(SPECIFY BELOW)*:

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
☐ TYPE A OR B NDA REVIEW ☐ END OF PHASE II MEETING ☐ CONTROLLED STUDIES ☐ PROTOCOL REVIEW ☐ OTHER (SPECIFY BELOW):	☐ CHEMISTRY REVIEW ☐ PHARMACOLOGY ☐ BIOPHARMACEUTICS ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE IV STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL-BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

- ☐ PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS:

Hi Mary,

This is a RiskMapp the sponsor sent with their original application regarding NDA 22-411. The PDUFA date is July 18, 2009. Please review the attached RiskMapp and let me know if you have any comments. I also attached labeling provided by the sponsor that includes the MedGuide. I can be reached at either william.bender@fda hhs.gov or 301-796-2145.

Thanks,

Bill

SIGNATURE OF REQUESTER	METHOD OF DELIVERY (Check one)
CDR Bill Bender, RPh. Consultant Regulatory Project Manager 301-796-2145 william.bender@fda hhs.gov	☐ MAIL ☐ HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

21 pages withheld immediately after this page as B4 (Draft Labeling)

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/s/

Thomas Laughren
9/25/2008 02:56:57 PM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

TO *(Division/Office)*:
CDER OSE CONSULTS

FROM: HFD-130/Division of Psychiatry Products

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
09/24/2008		22-411	NDA submission	09/18/2008

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
Trazodone Contramid OAD Extended-Release Caplets		Major Depressive Disorder	PDUFA due date of 07/18/2009

NAME OF FIRM: Labopharm

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE/ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE--NDA MEETING
- ☐ END OF PHASE II MEETING
- ☐ RESUBMISSION
- ☐ SAFETY/EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☐ OTHER *(SPECIFY BELOW)*: **Trade name review**

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
☐ TYPE A OR B NDA REVIEW ☐ END OF PHASE II MEETING ☐ CONTROLLED STUDIES ☐ PROTOCOL REVIEW ☐ OTHER (SPECIFY BELOW):	☐ CHEMISTRY REVIEW ☐ PHARMACOLOGY ☐ BIOPHARMACEUTICS ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE IV STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL-BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

- ☐ PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS: Attached to this consult is the proposed container label and carton labeling for this product. The sponsor also submitted a tradename (Oleptro) and a tradename review by the consultant firm, (b) (4) (also attached)

PDUFA DATE: 07/18/2009
ATTACHMENTS: Draft Package Insert, Container and Carton Labels
CC: Archival IND/NDA IND 76,137
HFD-130/Division File
HFD-130/RPM
HFD-130/Reviewers and Team Leaders

NAME AND PHONE NUMBER OF REQUESTER	METHOD OF DELIVERY (Check one)
CDR Bill Bender, RPh., Consultant Regulatory Project Manager	☐ DFS ONLY ☐ MAIL ☐ HAND

301-796-2145	
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

5/28/05

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/s/

Thomas Laughren

9/25/2008 02:55:58 PM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADM NISTRATION

REQUEST FOR CONSULTATION

TO *(Division/Office)*:			FROM:	
HFD- 860/Biopharm Attention: Ray Baweja			HFD-130/ Division of Psychiatry Products	
DATE 09/22/2008	IND NO.	NDA NO. 22-411	TYPE OF DOCUMENT NDA submission (505b2)	DATE OF DOCUMENT 09/18/2008
NAME OF DRUG Trazodone Contramid	PRIORITY CONSIDERATION PDUFA date of July 18, 2009		CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE **April, 2009**

NAME OF FIRM: Labopharm Canada

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE/ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE--NDA MEETING
- ☐ END OF PHASE II MEETING
- ☐ RESUBMISSION
- ☐ SAFETY/EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☐ OTHER *(SPECIFY BELOW)*:

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
☐ TYPE A OR B NDA REVIEW ☐ END OF PHASE II MEETING ☐ CONTROLLED STUDIES ☐ PROTOCOL REVIEW ☐ OTHER (SPECIFY BELOW):	☐ CHEMISTRY REVIEW ☐ PHARMACOLOGY ☐ BIOPHARMACEUTICS ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE IV STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL-BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

- ☐ PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
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- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS:

This is a 505(b)(2) NDA submission for Trazodone Contramid. The PDUFA due date is July 18, 2009, I have attached the link for the electronic portion of the submission: **\\FDSWA150\NONECTD\N22411\N_000\2008-09-18. There are also paper portions of the submission.**

SIGNATURE OF REQUESTER	METHOD OF DELIVERY (Check one)
CDR Bill Bender Regulatory Project Manager 301-796-2145 william.bender@fda.hhs.gov	☐ MAIL ☐ HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

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/s/

William Bender

9/22/2008 12:35:01 PM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADM NISTRATION

REQUEST FOR CONSULTATION

TO *(Division/Office)*:			FROM:	
HFD- 710/Stat			HFD-130/ Division of Psychiatry Products	
DATE 09/22/2008	IND NO.	NDA NO 22-411.	TYPE OF DOCUMENT NDA submission (505b2)	DATE OF DOCUMENT 09/18/2008
Trazodone Contramid	PRIORITY CONSIDERATION **PDUFA due date is July 18, 2009**		CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE **April, 2009**

NAME OF FIRM: Labopharm Canada

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE/ADDITION
- ☐ MEETING PLANNED BY
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- ☐ RESUBMISSION
- ☐ SAFETY/EFFICACY
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- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☐ OTHER *(SPECIFY BELOW)*:

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
☐ TYPE A OR B NDA REVIEW ☐ END OF PHASE II MEETING ☐ CONTROLLED STUDIES ☐ PROTOCOL REVIEW ☐ OTHER (SPECIFY BELOW):	☐ CHEMISTRY REVIEW ☐ PHARMACOLOGY ☐ BIOPHARMACEUTICS ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE IV STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL-BIOPHARMACEUTICS
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IV. DRUG EXPERIENCE

- ☐ PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
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- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS:

This is a 505(b)(2) NDA submission for Trazodone Contramid. The PDUFA due date is July 18, 2009, I have attached the link for the electronic portion of the submission: **\\FDSWA150\NONECTD\N22411\N_000\2008-09-18. There are also paper portions of the submission.**

SIGNATURE OF REQUESTER	METHOD OF DELIVERY (Check one)
CDR Bill Bender, RPh Regulatory Project Manager 301-796-2145 william.bender@fda.hhs.gov	☐ MAIL ☐ HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

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/s/

William Bender

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